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A persistent flu-like syndrome in patients treated with erythropoietin

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SINDROME «FLU-LIKE» PERSISTENTE EN PACIENTES TRATADOS CON ERITROPOYETINA

RESUMEN

En cinco de diez pacientes tratados con eritropoyetina humana recombinante (EPO) se observó un síndrome «flu-like», que en dos de ellos apareció hace más de veinticuatro meses y persiste en la actualidad. Este síndrome «flu-like» de larga duración es muy poco habitual y en la literatura sólo se refieren casos que duraron pocas semanas tras la iniciación del tratamiento con EPO. En nuestros pacientes se pudo conseguir una ligera remisión de los síntomas reduciendo las dosis y prolongando el tiempo de administración (cinco horas). La sintomatología pudo ser fácilmente atenuada mediante la administración de 500 mg de aspirina. Debe remarcarse que durante los ocho meses que duró el tratamiento con EPO los síntomas y signos del síndrome no variaron. Se excluyeron otras causas de malestar, como infecciones generales, reacciones por pirógenos u otros fenómenos alérgicos. Concluimos que el tratamiento de elección en los pacientes tratados con EPO con un síndrome «flu-like» persistente es la administración de EPO en una única dosis semanal aplicada durante un período de tiempo prolongado y añadiendo aspirina al tratamiento. Los mecanismos que inducen este síndrome parecen estar mediados por prostaglandinas, puesto que los síntomas responden al tratamiento con aspirina.

Palabras clave: ***Eritropoyetina humana recombinante (EPO). Síndrome «flu-like». Tratamiento. Aspirina. Alergia. Reacciones por pirógenos. Infecciones generalizadas.***

SUMMARY

In five out of ten patients treated with recombinant human erythropoietin (r-HuEPO) we observed a flu-like syndrome which persisted in two of them for up to 24 months now. This long-lasting flu-like syndrome is fairly unusuable, as in the literature it is reported to persist only for a few weeks after the initiation of r-HuEPO treatment. In our patients, a slight relieve of symptoms could be achieved when the dosage was reduced and the application occurred over a prolonged period of time (five hours). Symptoms could easily be mitigated by administering 500 mg of aspirin. It is of note that during the eight months of r-HuEPO treatment the symptoms and signs of the syndrome did not change. Other causes of malaise like general infections, pyrogenic reactions or other allergic phenomena could be excluded. We conclude that in r-HuEPO treated patients suffering from a persistent flu-like syndrome the treatment of choice is to administer r-HuEPO in a single weekly dose,

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which is given over a prolonged period of time and to add aspirin on the days of r-HuEPO application. The underlying mechanism of the syndrome seems to be prostaglandin mediated, as the symptoms respond to aspirin treatment.

Key words: ***Recombinant human erythropoietin (r-HuEPO). Flu-like syndrome. Treatment. Aspirin. Allergy. Pyrogenic reactions. Generalized infections.***

Recombinant human erythropoietin (r-HuEPO) is a highly efficient drug for the treatment of renal anemia. Since the introduction of r-HuEPO, however, a considerable number of unwanted side-effects has been reported (table I). These side-effects did not only occur in humans but also in animals [6, 7]. One of the adverse side-effects in patients treated with r-HuEPO is a so-called flu-like syndrome. This syndrome is characterized by a rise in body temperature, bone and muscle pain, chills and malaise. In r-HuEPO treated patients this syndrome has been described to occur early after the initiation of the r-HuEPO therapy, appearing fairly immediately after the application of r-HuEPO and subsiding completely within a few hours. Most often it disappears after several weeks of treatment with r-HuEPO. In our group of patients (n = 31) we observed a group of five patients exhibiting this syndrome. While in three patients the symptoms disappeared within a few weeks of treatment, it persisted in two patients for 24 treatment months now. In this report, the data of these two patients will be presented.

Case 1: A 54 year old woman on dialysis for 14 years (underlying renal disease: pyelonephritis) received r-HuEPO for severe renal anemia. The indication for r-HuEPO treatment was that each transfusion, required every four weeks, resulted in anaphylactic reactions due to irregular antibodies. The r-HuEPO treatment was efficient in improving renal anemia as depicted in figure 1. Initially, the patient received 120 u r-HuEPO/kg b.w. One week after the start of therapy, she reported a rise of body temperature up to 39° C. Temperature rose immediately after the bolus injection of r-HuEPO, topping three hours later and subsiding afterwards. At the same time malaise, chills and bone and muscle pain occurred. Applying the same amount of r-HuEPO as an infusion over five hours resulted in a slight relieve to the patient. As treatment with r-HuEPO was needed urgently, we continued therapy. In a first step we halved the amount of r-HuEPO. This procedure only slightly reduced the symptoms. In a next step, the dosage was reduced to 40 u/kg b.w. resulting in a further reduction of the symptoms. Now no malaise, muscle pain and chills were observed, when only 40 U were applied as a continuous infusion over five hours. However, temperature still rose up to 38.5° C.

No other patient in that dialysis shift developed any symptoms of pyrogenic reactions. Regularly obtained blood cultures exhibited no contamination. Furthermore, we started to test whether r-HuEPO really induced the temperature by infusing in a blinded random manner r-HuEPO or saline only. The resulting reports from the patient and the measurement of the temperature clearly demonstrated that only when r-HuEPO was administered, temperature rises occurred (fig. 2 a + b). The slight temperature rise in figure 2b is due to the warming up of the dialysate.

As the patient still complained of the flu-like syndrome and the hemoglobin concentration was decreasing slowly (fig. 2), we decided to administer r-HuEPO once a week and to increase the dosage. Again r-HuEPO was infused for five hours during the dialysis session. In addition, the patient was given 500 mg of aspirin immediately after the dialysis, and she as advised to take another 500 mg three hours later, if symptoms occurred. This regimen was well tolerated and accepted by the patient.

Case 2: A 33 year old woman on dialysis for 4 years (underlying renal disease: lupus erythematodus) was elected to receive r-HuEPO for the treatment of renal anemia (blood transfusions every six weeks). Also in her the treatment was efficient (fig. 1). Symptoms and signs of a flu-like syndrome and the time course were similar to that of patient 1. The two patients, however, were in different dialysis shifts and did never meet.

Also in this patient we administered r-HuEPO and saline in a blinded random sequence. This also revealed that during the r-HuEPO application there was only a slight rise in body temperature, though not that pronounced as in case 1 (fig. 2 c + d). Malaise, however, was much more pronounced in that patient. Again no other patient of that dialysis shift exhibited signs of pyrogenic reactions, and blood cultures were also negative.

As in the other patient, we decided to administer r-HuEPO in a single dose per week. Like in case 1, this patient was given 500 mg of aspirin immediately after the dialysis session and advised to take another 500 mg three hours later, if symptoms occurred. Also this patient found this way of r-HuEPO application acceptable.

Discussion

Flu-like syndrome is a well-known side-effect of treatment with r-HuEPO (table I). In general, however, this syndrome only occurs for a short period of time

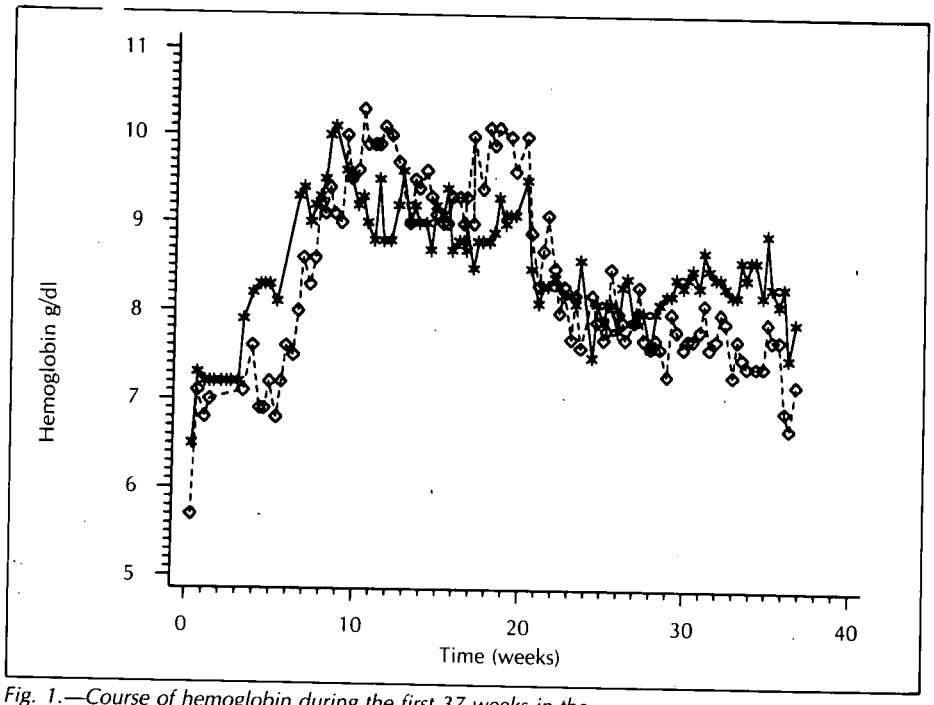
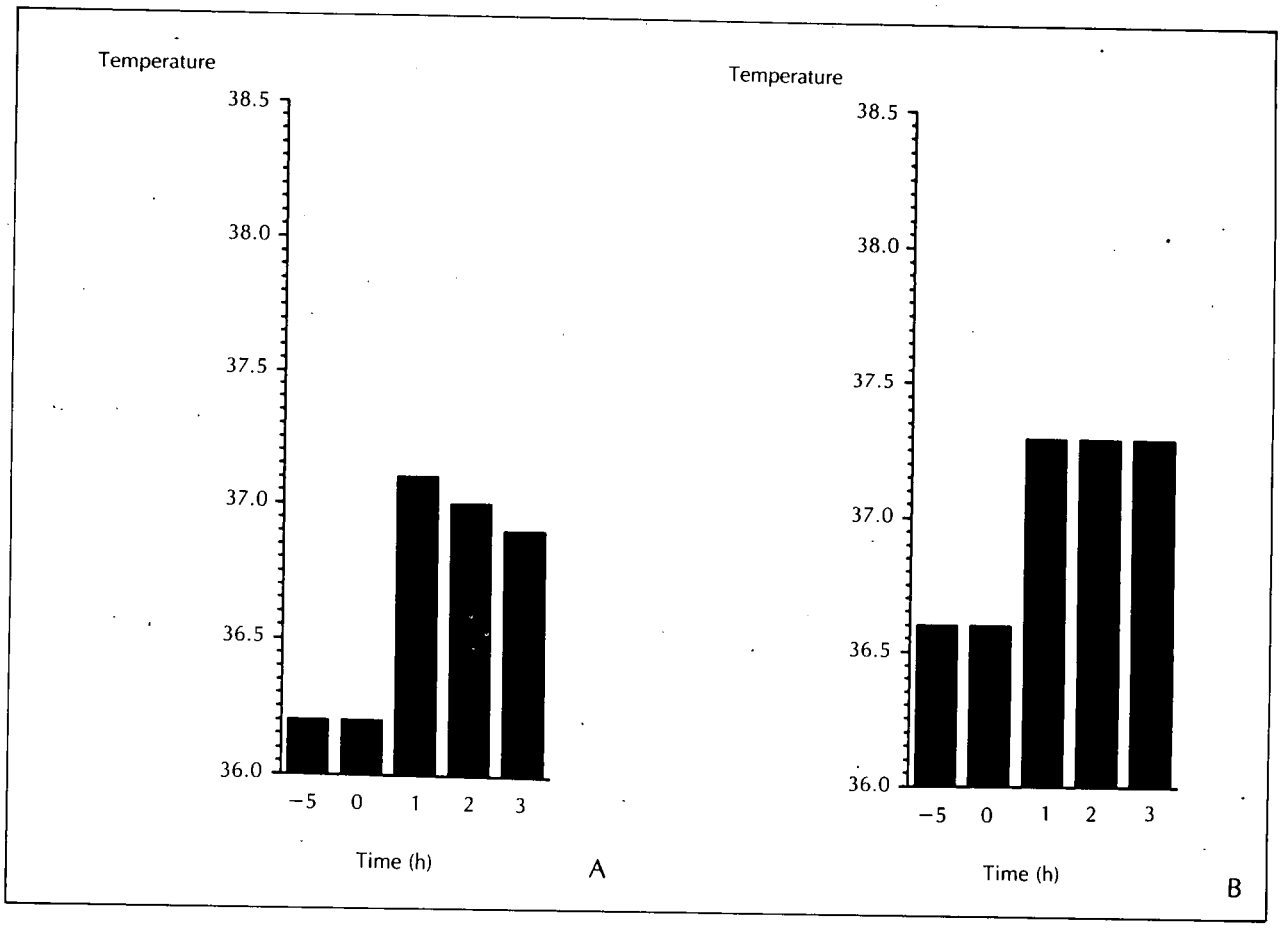


Fig. 1.—Course of hemoglobin during the first 37 weeks in the 2 patients (case 1: broken line; case 2: solid line).



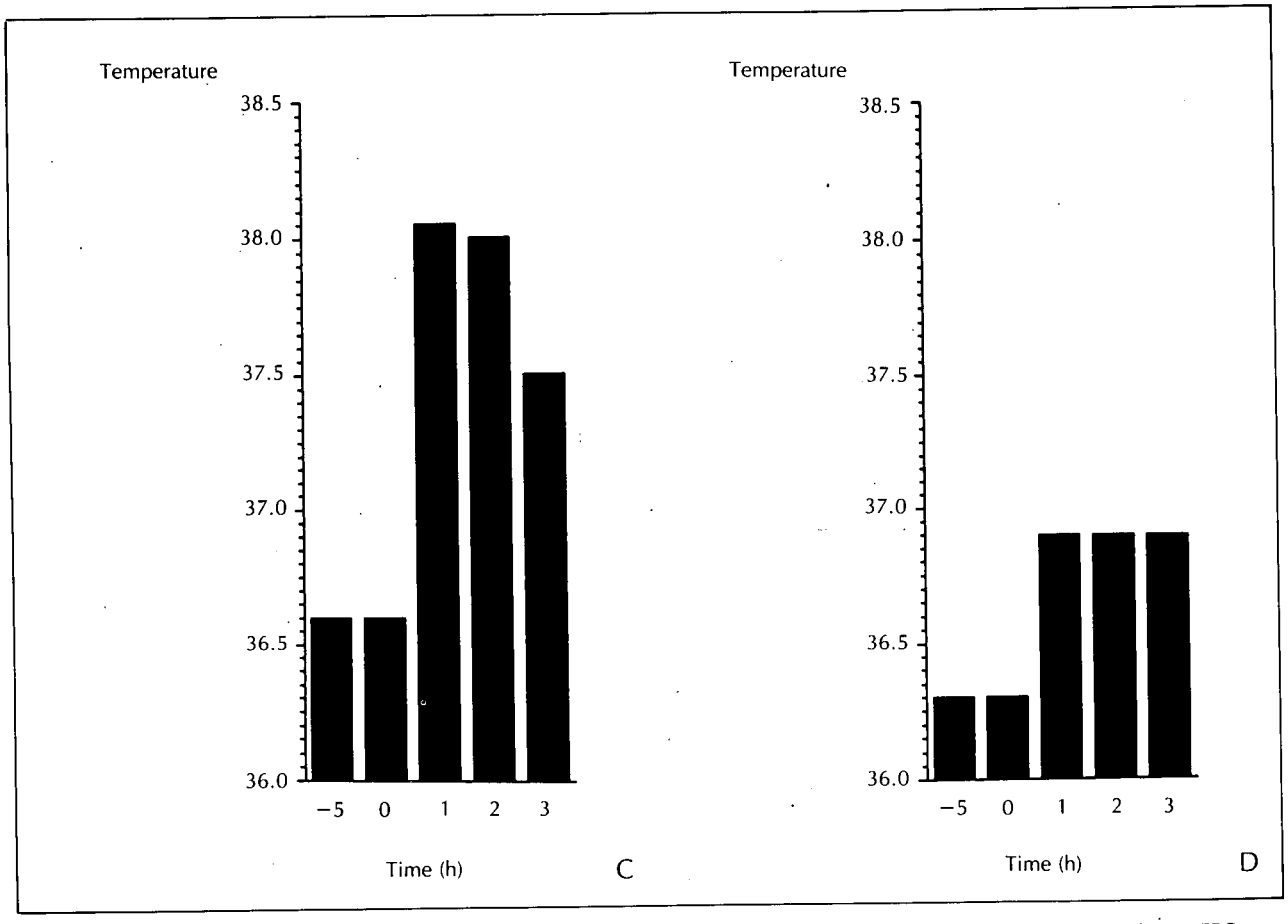


Fig. 2.—Median temperature values 5 hours before the start of hemodialysis, at the end and during the following 3 hours in our patients. The data were taken from 20 blinded applications per patient of either r-HuEPO or saline. a: case 1, with r-HuEPO; b: case 1, no r-HuEPO; c: case 2, with r-HuEPO; d: case 2, no r-HuEPO.

Table I. Number of patients suffering from adverse side-effects of r-HuEPO

Author	Total	BP	BC	Flu	Thro
Bommer[1]	32	8	4	?	+
Casati[2]	14	8	2	5	?
Creutzig[3]	16	7	?	?	?
Eschbach[4]	25	4	?	?	?
Graf[5]	9	4	?	> 4	−
Grützmacher[8]	92	?	5	8	−
Jacquot[9]	28	5	?	?	?
Rhyner[10]	72	9	5	r	?
Samtleben[11]	92	27	?	?	?
Schaefer[12]	15	3	2	3	+
Stutz[13]	8	?	3	?	+
Wilkström[14]	12	r	?	r	?
Winearls[15]	10	r	2	4	?

Total: number of patients under study; BP: rise in blood pressure; BC: thrombosis of the fistula; flu: flu-like syndrome; thro: thrombocytosis; r: rare; ?: not mentioned; −: not observed.

mainly after the initiation of this type of treatment. The number of patients found in different studies to exhibit this syndrome is also highly variable (table I). We suggest that a careful examination and questioning would reveal considerably more patients suffering from this adverse side-effect. Up to now, no flu-like syndrome in r-HuEPO treated patients lasting for up to 24 months has been reported. In our patients, no other cause for a flu-like syndrome could be found. This is demonstrated by negative blood cultures, the blinded random saline/r-HuEPO infusion and the fact that no «pyrogenic» reaction occurred in any patient of the same dialysis shift. Also signs of general infections were absent in our patients.

Up to now, there is no definite explanation for the occurrence of the reported flu-like syndrome. Allergic reactions seem not to be involved as the IgE-levels in our patients were not increased.

Furthermore, no eosinophilic cells were found in the white blood count. Allergic reactions might occur either due to r-HuEPO per se or the buffer solution. As no dramatic drop in hemoglobin production and no r-HuEPO antibodies were observed in our patients, this seems not to be the case in our patients. Furthermore, the quality of symptoms and signs did not change over

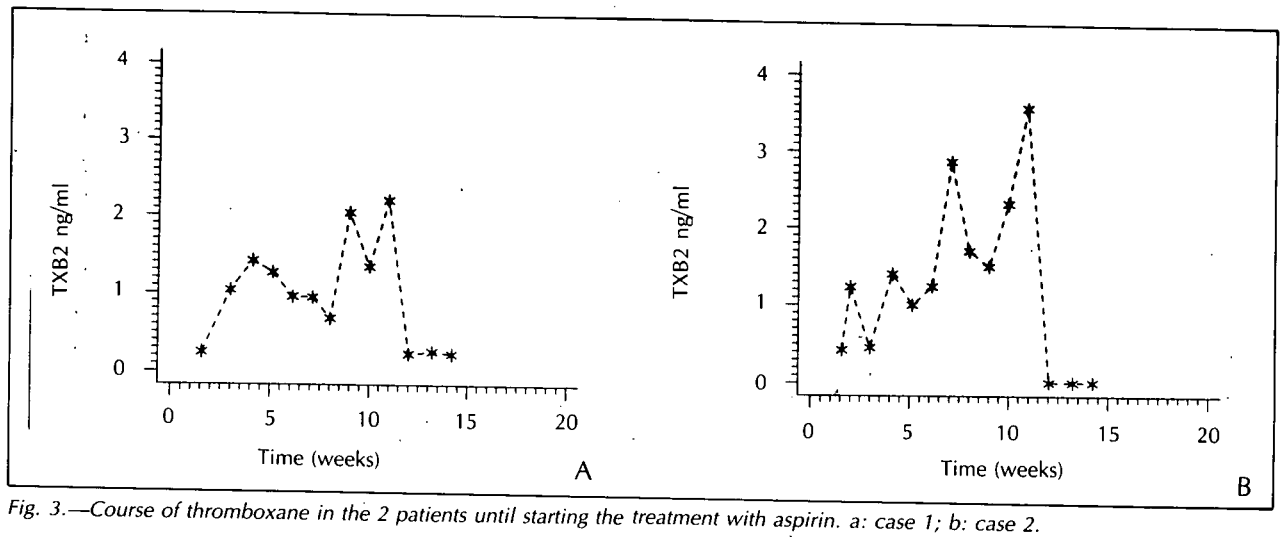


Fig. 3.—Course of thromboxane in the 2 patients until starting the treatment with aspirin. a: case 1; b: case 2.

time, which would be expected if there had been an allergic reaction either towards r-HuEPO or the buffer solution. Another possibility to explain the flu-like syndrome would be to persume that a prostaglandin mediated reaction, independent of the underlying mechanism, occurred. That prostaglandins might be involved is underlined by our finding that thromboxane increased in our patients (fig. 3). This notion is further supported by the finding that aspirin application abolishes the symptoms.

We conclude that in hemodialysis patients, in need of r-HuEPO treatment, but suffering from flu-like syndrome, the treatment of choice is to administer r-HuEPO in a single weekly dose, which is given over a prolonged period of time and to add aspirin on the days of r-HuEPO application. The underlying mechanism of the syndrome seems to be prostaglandin mediated, as the symptoms respond to aspirin treatment.

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