INCREASE OF THE BIOAVAILABILITY OF INTRAPERITONEAL ERYTHROPOIETIN IN CHILDREN ON PERITONEAL DIALYSIS BY ADMINISTRATION IN SMALL DIALYSIS BAGS

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Objective: To establish the effectiveness of administration of erythropoietin intraperitoneally in a small amount of fluid in children with renal anemia on continuous ambulatory peritoneal dialysis (CAPD).

Design: Prospective study in which children with renal anemia on CAPD were treated with erythropoietin intraperitoneally, administered in a specially designed bag containing 50 mL NaCl 0.9%.

Setting: University hospital.

Patients: The patient population consisted of 9 children treated with CAPD and 1 treated with nightly intermittent peritoneal dialysis. The median age was 7.8 years (range 4.1 - 15.2). Four of these children had not been treated with erythropoietin before (group A), and 6 had been treated with erythropoietin administered intraperitoneally in 250 mL of dialysis fluid (group B).

Interventions: Patients in group A started on a dose of approximately 300 units/kg per week (group A). Patients in group B received their previous dose. Dosage was adjusted to achieve a target hemoglobin level of 6.5 - 7.0 mmol/L (104 - 112 g/L). Serum ferritin levels and transferrin saturation were monitored and iron suppletion was prescribed in the case of iron deficiency.

Main outcome measures: Weekly erythropoietin dose in relation to hemoglobin level.

Results: In group A, median hemoglobin level rose from 5.3 mmol/L (85 g/L) to 6.6 mmol/L (106 g/L) after 6 months of therapy, whereas the median erythropoietin dose decreased from 266 to 234 U/kg/week. In group B, hemoglobin levels remained stable and median erythropoietin dose decreased from 262 to 194 U/kg/week. One patient in this group, for unknown reasons, never responded to erythropoietin treatment. He was excluded from further analysis. In the remaining 5 patients the median cumulative erythropoietin dose was 3250 U/kg in the 3-month period prior to the start of the study and 2713 in the 3-month period starting 6 months after the beginning of the study. This difference of 17% was statistically significant using a Wilcoxon test (p < 0.05).

Conclusion: Intraperitoneal administration of erythropoietin in a small amount of dialysis fluid leads to a decrease in the required dose.

KEY WORDS: Children; erythropoietin; intraperitoneal administration.

In children treated with continuous ambulatory peritoneal dialysis (CAPD) renal anemia can be effectively treated with erythropoietin administered intraperitoneally (IP) (1). A major advantage, as opposed to subcutaneous administration, is the avoidance of painful injections. A disadvantage is the necessity of a higher dose, which is related to a lower biological availability. To maximize resorption, erythropoietin is usually administered in the smallest commercially available bag of 250 mL during a prolonged dwell (10 - 12 hours). In a previous study we compared the pharmacokinetics of erythropoietin after subcutaneous and IP administration in children on CAPD (2). It was established that resorption after IP administration, measured as area under the curve, was similar to resorption after subcutaneous administration if erythropoietin was administered IP in 50 mL of dialysate. In this article we present the results of a therapeutic study in which erythropoietin was administered this way, using a specially designed 50 mL bag.

PATIENTS AND METHODS

Children on CAPD or nightly intermittent peritoneal dialysis (NIPD) already treated with IP erythropoietin and those in whom erythropoietin therapy was started entered the study. The study was performed between October 1994 and December 1995. Two patients were not eligible for further evaluation, one because no exact data were available on previous treatment with erythropoietin and the other because the hemoglobin levels were being main-
tained higher than usual in this child, whose parents were Jehovah's witnesses.

The study population consisted of 10 children (4 girls, 6 boys). Nine children were treated with CAPD, 1 with NIPD. The median age of these children was 7.8 years (range 4.1 – 15.2). Causes of renal failure were: renal dysplasia, posterior urethral valves, hereditary uremic syndrome, congenital nephrotic syndrome, interstitial nephritis, focal glomerulosclerosis, anti-GBM (glomerular basement membrane) glomerulonephritis, hereditary acro-osteolysis, and unknown. The children had been treated with CAPD for a median period of 14 months (range 0 – 80).

Four children (group A) had had no previous treatment with erythropoietin. Median hemoglobin level was 5.3 mmol/L (range 4.3 – 5.7) [85 g/L (range 68 – 91)] in this group. Hemoglobin levels for children without end-stage renal disease ranged between 7.1 mmol/L (114 g/L) and 9.0 mmol/L (144 g/L) in our laboratory. In the children of group A, erythropoietin was started at a dose of approximately 300 units per kilogram per week, administered 3 times per week.

Six children (group B) had been treated previously with erythropoietin, administered IP in the smallest commercially available bag (250 mL). These patients had been on erythropoietin for a median period of 28 months (range 7 – 65). Their median hemoglobin level was 6.6 mmol/L (range 4.5 – 7.3) [106 g/L (range 72 – 117)] at the start of the study. Median erythropoietin dosage was 262 U/kg/week (range 154 – 545) in these patients when they entered the study. Five of 6 patients received erythropoietin 3 times per week, whereas one of them was on a twice-a-week schedule. Dose and schedule were not changed when these patients entered the study.

Erythropoietin (Recormon, Boehringer Mannheim GmbH, Almere, The Netherlands) was administered in dialysis bags which were specially made for this purpose (Baxter BV, Utrecht, The Netherlands). These bags contained 50 mL NaCl 0.9% solution. The parents injected erythropoietin into the bags themselves; they were carefully trained to do this by a member of the nursing staff. The bags, equipped with a UV-flash port, were instilled after complete drainage of the abdomen for a 10- to 12-hour dwell. In patients on CAPD erythropoietin was administered overnight, while this was done during the day in the patient on NIPD.

The target hemoglobin level was 6.5 – 7.0 mmol/L (104 – 112 g/L) in both groups. Dosage was adjusted every 2 months. As long as the target level was not reached erythropoietin dosage was increased by 75 U/kg/week. Dosage was decreased by 75 U if the hemoglobin concentration exceeded 7.0 mmol/L (112 g/L). Hemoglobin, hematocrit, and the number of reticulocytes were assessed every 2 weeks. Serum ferritin levels and transferrin saturation were assessed every 2 months, and iron supplementation was prescribed if there was evidence of iron deficiency (serum ferritin below 100 µg/L; transferrin saturation below 20%).

### RESULTS

In group A, 2 children were treated for a period of 7 months, while 2 were treated for a period of 11 months. In all patients hemoglobin levels increased after the start of therapy. The median hemoglobin level after 6 months was 6.6 mmol/L (range 6.2 – 7.5) [106 g/L (range 99 – 120)]. No blood transfusions were needed. In the 2 patients who remained on therapy for 11 months, final hemoglobin levels were 8.0 mmol/L (128 g/L) and 8.1 mmol/L (130 g/L). The median starting dose was 266 U/kg/week (range 235 – 293). After 6 months of therapy the median dose was reduced to 234 U/kg/week (range 100 – 294). The final dose was 238 and 176 U/kg/week in the 2 patients who remained on therapy for 11 months.

In group B, children were treated for a median period of 11 months (range 6 – 12). Hemoglobin levels remained stable during the study (Figure 1). The median hemoglobin level was 6.8 mmol/L (range 5.8 – 7.9) [109 g/L (range 93 – 126)] 6 months after the start of the study. Erythropoietin dosage and range is given in Figure 2. The median dosage was 262 U/kg/week at the start of the study and 194 after 6 months of therapy.

The range of erythropoietin dose was very broad. This was mainly due to a very high dosage of 545 U/kg/week in 1 patient. This patient had started on erythropoietin 7 months prior to the start of the study and never reached satisfactory control of renal anemia, in spite of a high dose. This child was the only one to receive blood transfusions during the study period (Figure 1). He received a kidney transplant 6 months after entering the study. This patient seemed to be resistant to erythropoietin therapy; an explanation for this was not found. There was no iron deficiency (serum ferritin >1000 µg/L), folic acid levels were within the normal limits, and there was no reason to assume that the patient suffered from infections.

The patient described above was excluded from the following statistical analysis because it is impossible to compare two modes of erythropoietin administration in a patient who does not respond to the drug and who receives blood transfusions. Erythropoietin dosage was stable in the months prior to the start of the study and was stabilized again 6 months after the start of the study in the other 5 patients. The cumulative dose from T-2 to T0 (the 3-month period before the start of the
study) as well as the area under the curve from T7 to T9 (the 3-month period after reaching a stable erythropoietin dose) was calculated in these patients. Median cumulative dose for a 3-month period decreased from 3250 U/kg (range 2002 – 5577) to 2713 (1690 – 3393). The cumulative dose decreased in all patients. The median decrease in the cumulative dose was 17% (range 5 – 45). The difference between the cumulative dose before and after the switch to erythropoietin administration in a small dialysate volume was statistically significant (Wilcoxon; p < 0.05).

**DISCUSSION**

In patients treated with CAPD, renal anemia can be effectively treated with erythropoietin. Two modes of administration have been used successfully, subcutaneous administration and IP administration.

Studies in adults have demonstrated that subcutaneous administration is very effective, with doses of 100 to 150 U/kg/week (3,4). In children, a mean maintenance dose between 74 and 210 U/kg/week has been reported (5–11). In children there seems to be an influence of age on the dosage needed, with younger children needing a higher dose (12).

Intraperitoneal administration has proven to be an alternative method of treatment. The major advantage of this mode of treatment is the fact that there is no need for painful injections. The major disadvantage is the higher maintenance dose. In a study in adults the mean maintenance dose was 225 – 255 U/kg/week (13). Our group has reported a mean maintenance dose of 279 U/kg/week in a group of 16 children on CAPD (1). In this study erythropoietin was added to the smallest commercially available bag containing 250 mL dialysis fluid. Lower doses of 100 – 150 U/kg/week were reported in a small group of 3 children, 2 of whom received erythropoietin in a small volume of only 20 mL (14).

Biological availability is determined by the amount of dialysis fluid to which erythropoietin is added (15). We established that the resorption of erythropoietin after IP administration, measured as area under the curve, is similar to resorption after subcutaneous administration if erythropoietin is added to a small volume of only 50 mL of dialysate (2).

In the present study, 10 children were treated with erythropoietin administered IP in such a small volume. In 4 children who had not been previously treated with erythropoietin, the median dosage was 234 U/kg/week after 6 months of therapy. In 6 children who had been treated with erythropoietin IP in 250 mL of dialysis fluid, the median dosage could be decreased from 262 to 194 U/kg/week.

These data are consistent with the hypothesis that the administration of erythropoietin in a small volume will lead to increased resorption and a decrease in the dose. Decreasing dialysis volume to 50 mL 3 times per week during the night will lead to the absence of dialysis during these periods. During the period in which the study was performed, another study was done looking at weekly Kt/V and creatinine clearance (16). In a group of 19 children a mean Kt/V of 2.31 was found, which is higher than values reported for most adult groups. Since target values for Kt/V are not yet clearly defined for children, Kt/V cannot be used to establish, in the individual patient, whether or not a decrease in dialysis is possible.
During this study we did not see clinical problems as a result of the decrease in dialysis volume. If we had, NIPD, with administration of erythropoietin during the day, may have been a solution.

Administration of erythropoietin once-a-week instead of 3 times per week is probably not the right way to increase dialysis. We performed a study in 6 children who had been successfully treated with erythropoietin IP, added to 250 mL of dialysis fluid, 3 times per week (17). In these children, erythropoietin was administered in the same weekly dose, once-a-week instead of 3 times per week. This was not effective, since hemoglobin levels started to decrease rapidly.

Contamination is a risk if medication is added to the dialysis fluid. During our previous study, in which erythropoietin was given IP added to a bag containing 250 mL of dialysis fluid, we saw one peritonitis episode every 14.7 patient-months. In 1995, the year in which the present study was performed, the peritonitis incidence was once every 12.6 patient-months, which is within the expected variation.

It can be concluded that intraperitoneal administration of erythropoietin in a small amount of dialysis fluid leads to a decrease in the required dose.

Although the observed decrease in dose does seem real, the question remains whether it is clinically significant. A median decrease of 17% in the need for erythropoietin was established. Although this does not seem much in terms of percentage, savings can amount to significant sums if it can be applied on expensive drugs such as erythropoietin. The commercial production of small bags for the purpose of drug administration may become even more interesting if other drugs such as growth hormone become available for IP administration.

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