Efficacy prospective study of different frequencies of Epo administration by i.v. and s.c. routes in renal replacement therapy patients

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Abstract

Background. The problem of pure red cell aplasia (PRCA) prompted nephrologists to revert to a wider intravenous (i.v.) utilization of erythropoietin (Epo). Once weekly i.v. Epo administration has been suggested to be as effective as the twice/thrice weekly i.v. dose. The aim of the present study was to test whether once weekly i.v. Epo administration is equally as cost-effective as once weekly subcutaneous (s.c.) and 2–3 times weekly i.v. administration.

Methods. We prospectively studied 41 patients (23 males, aged 28–82 years), on renal replacement therapy for 18–286 months, stabilized on twice or thrice weekly s.c. Epo-\textsuperscript{a} (basal). The patients were treated for three consecutive 6 month periods with once weekly s.c. (OWSC), once weekly i.v. (OWIV) and twice/thrice weekly i.v. (TWIV) Epo-\textsuperscript{a}. The initial dose for each period was equal to the final dose of the previous one; when necessary, the dose was adjusted according to DOQY guidelines. Iron, folic acid and vitamin B\textsubscript{12} suppletions were given throughout all the study periods. At the end of each of the four study periods, the following parameters were evaluated: haemoglobin, haematocrit, hypochromic red blood cells (RBCs), iron, serum ferritin, transferrin, folate, vitamin B\textsubscript{12}, C-reactive protein (CRP), Kt/V, parathyroid hormone (PTH) and weekly dose of Epo-\textsuperscript{a}.

Results. Thirty-three out of 41 enrolled patients completed the study (there were five deaths, two renal transplants and one transfer). No significant changes were observed as regards iron, serum ferritin, transferrin, folate, vitamin B\textsubscript{12}, CRP, Kt/V or PTH level. Haemoglobin levels were not different at the end of the basal (11.7±1.21), OWSC (11.8±0.86) and TWIV (12.1±1.04) periods, while significantly lower levels were observed after the OWIV period (11.0±0.97, \(P<0.01\)). Weekly Epo consumption (Epo U/week/kg body weight/g haemoglobin) was: basal 11.57±5.96; OWSC 10.22±4.53; OWIV 15.99±7.7\textsuperscript{*}; and TWIV 11.89±6.3\textsuperscript{**} (*\(P<0.01\) vs basal; \(\textsuperscript{*}P<0.01\) vs OWSC).

Conclusions. From our results, the OWIV schedule seems to have less efficacy in the control of anaemia of chronic renal failure patients on dialysis treatment than either OWSC or TWIV schedules.

Keywords: anaemia; chronic renal failure; erythropoietin

Introduction

Recombinant human erythropoietin (Epo) has represented a substantial advance in the treatment of anaemia of uraemic patients. Epo when administered by the subcutaneous (s.c.) route is on average 30\% more cost-effective than by the intravenous (i.v.) route [1–6]. Once weekly s.c. administration of Epo may be as effective as three times weekly s.c. administration at comparable weekly doses [7–9]. Against this background, s.c. administration has been the first choice route in haemodialysed patients, at least in European countries [10].

The recent problem of pure red cell aplasia (PRCA), mainly associated with the s.c. use of some brands of Epo [11,12], prompted European nephrologists to revert to the use of the i.v. route of Epo administration.

In order to maintain the enhanced compliance obtained with once weekly s.c. administration, a once...
weekly i.v. administration was suggested. As far as we know, only one study has directly compared the efficacy of once weekly i.v. vs once weekly s.c. Epo administration, demonstrating the equivalence of the two routes [13]. However, the treatment period of the above study lasted only 16 weeks.

In the present investigation, we wanted to test the efficacy of once weekly i.v. (OWIV) Epo administration in comparison with once weekly s.c. (OWSC) and two–three times weekly i.v. (TWIV) administration, with each treatment period lasting 24 weeks.

**Patients and methods**

**Patient selection criteria**

Patients were required to fulfil the following criteria: (i) age >18 years; (ii) extracorporeal dialysis treatment for >12 months; (iii) no serious adverse event, no known malignancies, no active infectious diseases and no inflammatory or haematological diseases at study entry; (iv) on twice/thrice weekly Epo administration for at least 6 months; (v) stabilized haemoglobin (Hb) levels >9.5 g/dl with unchanged Epo dosage and no blood transfusion in the last 3 months; (vi) consent to participate in the study.

The study was conducted according to the Declaration of Helsinki and was approved by the local ethical committee.

**Study design**

This was a single-centre, prospective sequential study designed to verify the effectiveness of OWIV administration of Epo-α as compared with OWSC and TWIV Epo administration.

All patients were stabilized on TWSC Epo therapy for at least 6 months. Then all patients were submitted to three study periods, each of 6 months: over the first period, Epo was administered once weekly by the s.c. route (OWSC); over the second period once weekly by the i.v. route (OWIV) and during the final period twice/thrice weekly by the i.v. route (TWIV). At the beginning of each period, the starting Epo weekly dose was equal to the mean weekly dose utilized in the last month of the preceding period. Thereafter, the dosage of Epo was adjusted in order to maintain Hb levels in the range between 11 and 12.5 g/dl, increasing or decreasing weekly Epo administration by 2000 IU for each 0.5 g/dl Hb reduction or increase outside the target range.

All patients were regularly supplemented with i.v. iron, folic acid and vitamin B<sub>12</sub> preparations.

The study started in February 2002 and ended in August 2003.

**Evaluated parameters**

Hb and haematocrit were evaluated every other week on blood collected before a midweek dialysis session. At the start of the study and the end of each period, the following parameters were measured: iron, transferrin saturation and ferritin blood levels; hypochromic red blood cells (RBCs; expressed as a percentage of total RBCs); folic acid and vitamin B<sub>12</sub> blood concentrations; intact parathyroid hormone (PTH) levels; ESR, C-reactive protein (CRP); and Kt/V, calculated by the Daugirdas method [14].

For the efficacy evaluation of the different treatment modalities, the mean weekly cumulative dose of Epo prescribed in the final month of each period was considered. The Epo dose was expressed as: total weekly dose (IU/week); total weekly dose normalized for body weight (IU/week/kg); and total weekly dose normalized for body weight and for the mean Hb serum levels in the final month of each study period (IU/week/kg/g Hb).

All severe adverse events, changes in concomitant medication and number of withdrawals from the study were recorded.

**Statistical analysis**

Descriptive statistics have been calculated for the considered variables.

The pattern of the target variable related to efficacy evaluation (total weekly dose of Epo; total dose normalized for body weight and total dose normalized for body weight and mean Hb levels) has been analysed taking into consideration the difference between the basal level and that at the end of each of the three investigated regimens by means of t-test for dependent samples. In addition, a covariance analysis was performed with age and the basal efficacy parameter value as covariates and with sex as a fixed factor. The drop-out patients have been included in the statistical model according to the intention to treat analysis; therefore, a statistical approach allowing for inclusion of missing data (proc mixed of SAS, release 8.2) has been used. A general linear model and random coefficient models have been fitted together with several patterns of the variance-covariance matrix. The linear model with a variance-covariance unstructured pattern has been chosen for its best fitting of the data according to the corrected Akaike’s information criterion. Thus, least squares means together with their SE have been estimated.

Multiple comparisons have been carried out by means of Scheffe’s procedure at a significance level adjusted accordingly for multiplicity.

Comparisons for non-normally distributed parameters were carried out by non-parametric tests (Friedman ANOVA for repeated samples).

Occurrence of adverse events and main clinical outcomes were compared by χ<sup>2</sup> test.

**Results**

Forty-one out of 78 patients treated in the central dialysis unit fulfilled the selection criteria and entered the study. The demographic characteristics of these patients are shown in Table 1. Thirty-three patients completed the study; five patients died, three during the OWIV period and two during the TWIV period. Causes of death were: cancer (one), sepsis (one), intestinal infarction (two) and myocardial infarction (one); during the TWIV period, two patients were transplanted and one patient was transferred to another centre.
The mean Hb and haematocrit levels of the last 2 months during each study period are shown in Figure 1. Hb and haematocrit levels overlapped substantially during the pre-study, OWSC and TWIV periods; during the OWIV period, Hb and haematocrit were significantly lower than in all other periods.

Table 2 shows the values of the main parameters measured at the end of each study period. No major difference was evident for any of the evaluated parameters.

The mean weekly Epo doses utilized in the last month of each period are shown in Figure 2. During the last month of the OWIV period, the mean weekly dose of Epo was significantly higher compared with the basal period and the other two study periods. This result was the same when we considered either all patients studied in each period or only the 33 patients who completed the study. Table 3 shows the complete comparison analysis by t-test for dependent samples for mean weekly Epo doses, normalized for both body weight and Hb value. Again, the Epo doses utilized during the OWIV period were significantly higher compared with each of the other treatment periods. The lowest doses were utilized during the OWSC period, even if the difference from TWIV was not significant.

During the OWIV period, Epo doses needed to be increased in 30 patients, reduced in three and remained unchanged in five.

When all the periods were considered cumulatively, a highly significant inverse relationship was found between stabilized Hb levels and Epo doses, normalized for body weight (Figure 3). The covariance analysis demonstrated that in addition to the schedule of Epo administration (\( F = 27.02, P < 0.001 \)), Hb levels at the start of the study were the only other factor affecting Epo doses (\( F = 28.7, P < 0.0001 \)). On the other hand, gender, age, aluminium levels, dialysis efficiency, time spent on dialysis and angiotensin-converting enzyme (ACE) inhibitor use do not seem to play any role.

During the study period, five patients needed blood transfusions (four patients for haemorrhagic events in the gastrointestinal tract and one patient due to arterio-venous fistula bleeding): two patients received blood transfusions during the OWSC period, one patient during the OWIV period, and two patients during the TWIV period.

Table 3 shows the incidence of the clinically relevant adverse events during the three study periods. No significant difference was evident for any adverse event.

Discussion

The introduction of recombinant human Epo therapy has greatly improved the clinical outcome of chronic renal failure patients [15–17], but has also substantially increased the economic cost of uraemic patient treatment. A great number of trials tried to determine the
Most of these studies reached the same conclusion that the s.c. route allows a 20–30% reduction of Epo dose as compared with the i.v. route [1–6]. Furthermore, some authors found that the once weekly schedule was as effective as twice/thrice weekly administration [8,9].

After the sudden increase in the reports of Epo-associated PRCA, almost exclusively associated with the s.c. use of some brands of Epo [11,12], their s.c. administration was forbidden in European countries. This prompted nephrologists to revert to a wider i.v. utilization of Epo in dialysis patients.

The once weekly i.v. administration schedule was suggested possibly to maintain the enhanced compliance obtained by the once weekly schedule. The main aim of our study was to verify whether the i.v. once weekly schedule could really be utilized on a cost-effectiveness basis.

From our results, we found that the OWSC schedule was at least as equally effective as the twice/thrice weekly schedule, as already known by previous studies [8,9]. On the other hand, our data do not confirm the equivalence of the OWIV schedule with either the TWIV or OWSC schedules. In fact, we found that during the OWIV period, Epo doses were consistently and significantly higher when compared with all the other treatment periods. Furthermore, in >70% of patients treated on the OWIV schedule, the Epo dose needed to be augmented in an attempt to maintain the Hb level within the prescribed levels. In addition, notwithstanding the increased Epo doses, during the same treatment period, Hb levels were slightly but significantly lower compared with all the other periods. Two previous studies have dealt with OWIV Epo administration [13,18]. The first of these studies, from Barré and co-workers [13], compared OWIV with TWIV Epo administration [13], suggesting equivalent effects of the two utilized schedules. The contradictory results of this study as compared with our data may be due to some substantial differences in the two studies. Our study protocol was a sequential one, with the same patients observed over all the three treatment periods. In the Barré study [13], patients were divided into two groups each submitted to a different treatment
protocol: 115 submitted to OWIV and 88 to OWSC. In our sequential study, each patient is the control for himself, which is the best way to minimize variance due to different patient characteristics, in the case of relatively small samples.

Secondly, our patients were submitted to three treatment periods, including the TWIV schedule. In the Barre study, the TWIV treatment was part of the pre-study period.

Thirdly, each period of our study lasted 6 months and only the stabilized Hb levels of the last 2 months for each period were taken into account for the comparison, minimizing a possible carry-over effect of the previous treatment schedule. In addition, the possibility of a carry-over effect is not very likely if we take into consideration that the treatment protocol with the poorest effect on Hb (OWIV) followed that with the best effect (OWSC).

In the Barre study, the dose adjustment period lasted only 12 weeks, with a further 4 week treatment period without dose adjustment. Even though in ~80% of these patients stable Hb levels were obtained, without any need for a major increase in Epo dose, in fact mean Hb concentrations were significantly lower at the end of the study period and mean weekly Epo doses were significantly higher.

In another study, Leikis and co-workers [18] studied a group of stable uraemic dialysis patients on Epo therapy who were randomly assigned to commence with either the s.c. or i.v. Epo route and after 3 months they were crossed-over to the alternative route. The authors confirmed a reduced effectiveness of the i.v. route as compared with the s.c. route of Epo administration. In this study, the doses and the schedules (once, twice or thrice weekly) of Epo administration were kept constant over the whole of the study in each patient and the levels of Hb were considered as the measure of treatment efficacy. Due to this specific design of the study, it is not possible to compare the data of the once weekly Epo administration with the twice/thrice weekly schedules of our study. Furthermore, also for this study, the treatment periods were substantially shorter than ours (3 vs 6 months).

The difference we observed among the different treatment schedules cannot be ascribed to different supplementations of iron, folic acid or vitamin B12 in our patients, since these variables were all well maintained within the normal range over all the study periods (Table 2). In addition, good dialysis efficiency (Kt/V) and PTH control were also obtained during the whole study, with no major changes in the inflammatory status, as indirectly evaluated by CRP levels.

The main finding of our study was that once weekly Epo administration works well only when given by the s.c. route, while the once weekly i.v. administration is matched by a substantial increase in the dose. Our findings are not surprising in our opinion, and are also welcome since it is widely recognized that the s.c. route provides 20–30% saving in Epo dose when administered on multiple weekly schedules [1–6]. K/DOQI guidelines also stressed the convenience of Epo administration on a two–three times per week basis [18].

The reason for the greater effectiveness of the s.c. route of Epo administration as compared with the i.v. route has been attributed to the longer half-life of the former [19–21] which might allow a prolonged interaction of Epo with its receptors on the erythroid progenitor cells [22]. This pharmacodynamic difference might even be amplified when the once weekly schedule is utilized, providing an answer as to why there is a >30% increase in the Epo consumption during the OWIV treatment period.
Another possible contributing factor to the reduced efficacy of the OWIV schedule might be the neocytolytic phenomenon. In physiological conditions, neocytolysis, first described in subjects exposed to microgravity [23], is a compensatory phenomenon which consists of an increased destruction of newly formed erythrocytes when RBC mass is increased and Epo levels are decreased.

It has been suggested that neocytolysis might also play a role in the anaemia of uraemic patients [24–26], especially after a high i.v. bolus Epo peak, which could induce the commitment and proliferation of erythroid precursors and is followed by a progressive reduction of Epo concentration under the threshold level sufficient to start the neocytolytic mechanism. The OWIV schedule may represent a typical condition where the above-described phenomena might occur.

In conclusion, our results confirm that the s.c. route can permit a once weekly schedule. On the other hand, from our data, we cannot confirm the suggestion that once weekly Epo administration by the i.v. route is an equally effective mode of treatment.

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