ARTICLE

A double-blind, randomized, crossover study of the local tolerability of erythropoietin alfa formulations in dialysis patients

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ABSTRACT

Objectives: A double-blind, randomized, crossover study was conducted to compare the local tolerability of subcutaneous injections of epoetin alfa formulated with a citrate buffer (epoetin alfa-C) versus epoetin alfa formulated with a sodium phosphate buffer (epoetin alfa-P).

Methods: The study utilized a 2-period, 2-treatment crossover design, with no washout period. Forty-eight dialysis patients were randomly assigned to receive 6 consecutive subcutaneous injections of epoetin alfa-C or epoetin alfa-P. After completing their first treatment period, patients were switched to the alternate therapy. The primary efficacy outcome was patient-evaluated pain assessed after each injection using a verbal descriptor scale (VDS) and a visual analog scale (VAS). The duration of injection-site discomfort and the degree of redness/ and itching were also assessed.

Results: At all evaluation time points, subjects rated pain consistently and significantly lower (e.g. VDS day 6, p=0.034; VAS day 6; p=0.023), and the duration of pain significantly shorter with epoetin alfa-P compared to epoetin alfa-C. However, further analysis detected a significant ($p \leq 0.10$) carryover effect in several time point comparisons, suggesting that these results be interpreted in light of possible carryover effects.

Conclusions: The results of this study indicate that epoetin alfa-P is associated with less, and shorter, injection-site discomfort than epoetin alfa-C.

Key words: citrate, dialysis, rhEPO; epoetin alfa; local pain; subcutaneous administration;

RÉSUMÉ

Objectifs : Étude randomisée, à double insu avec permutation visant à comparer la tolérance locale des injections sous-cutanées d'époétine alfa préparée avec un tampon de citrate (époétine alfa-C) à celle de l'époétine alfa préparée avec un tampon de phosphate de sodium (époétine alfa-P).

Méthodes : L'étude a été menée selon un modèle à deux temps, deux traitements avec permutation, sans période d'épuration thérapeutique. Au total de 48 patients ont été répartis au hasard pour recevoir six injections consécutives soit d'époétine alfa-C, soit d'époétine alfa-P). Après avoir complété leur première période de traitement, les patients ont simplement été permutés pour recevoir l'autre traitement. Le premier paramètre d'efficacité évalué a été la douleur telle que décrite par le patient après chaque injection, à l'aide de l'échelle de description verbale (VDS) et de l'échelle analogique visuelle (VAS). La durée de l'inconfort au point d'injection et le degré de la rougeur/des démangeaisons ont aussi été évalués.

Résultats : Pour tous les points dans le temps qui ont été évaluées, les patients ont coté l'intensité de leurs douleurs (p. ex., VDS au jour 6 : p = 0,034; VAS au jour 6 : p = 0,023) la durée de leurs douleurs comme étant significativement et constamment moindre avec l'époétine alfa-P qu'avec l'époétine alfa-C. Cependant, des analyses plus poussées ont décelé un effet différé significatif ($p \leq 0,10$) pour de nombreux points dans le temps qui ont été comparés, ce qui porte à croire que ces résultats doivent être interprétés à la lumière d'un probable effet différé.

Conclusions : Les résultats de cette étude indiquent que l'époétine alfa-P est associée à un inconfort au point d'injection, d'intensité et de durée moindres qu'avec l'époétine alfa-C.

Mots clés : citrate, dialyse, rhEPO, époétine alfa, douleur locale, administration sous-cutanée

INTRODUCTION

Anemia is a common problem in patients with chronic or end-stage renal disease undergoing hemodialysis and is caused primarily by a reduction in the secretion of erythropoietin, which plays an essential role in the regulation of red blood cell production.[1,2] Other factors that may contribute to anemia in this patient population include iron deficiency and blood loss.[1] Recombinant human erythropoietin (rhEPO) has been widely used for the treatment of anemia associated with chronic renal failure for more than a decade.[3,4] Initially, rhEPO was administered intravenously, but the discovery that the drug was also effective when administered subcutaneously led to the preferential use of this route in the majority of patients.[3-5] Among the potential advantages of subcutaneous rhEPO are the flexibility and convenience afforded by self-administration.[5-7] Subcutaneous rhEPO is effective not only when used in patients undergoing hemodialysis,[3-7] but also in those receiving chronic ambulatory peritoneal dialysis

(CAPD) and in those patients with renal insufficiency who have not yet started dialysis. [2-10]

One of the factors that has complicated subcutaneous rhEPO therapy in dialysis patients and affected patient compliance with long-term treatment, particularly in the case of self-administration, is local discomfort at the injection site.[11] It has been suggested that the citrate buffer contained in the subcutaneous epoetin alfa formulation may contribute to injection discomfort.[5] This raises the question of whether the local tolerability of subcutaneous injections of epoetin alfa might be improved by using sodium phosphate as the buffer. At the present time in Canada, all EPREX® pre-filled syringes and the EPREX 4,000 IU/mL single-use vials contain phosphate-buffered epoetin alfa. The EPREX 20,000 IU/mL multi-use vial contains citrate-buffered epoetin alfa.

The present double-blind, randomized, crossover study was conducted in dialysis patients to address this question by comparing the local tolerability of subcutaneous injections of epoetin alfa formulated with a citrate buffer (epoetin alfa-C) versus epoetin alfa formulated with a sodium phosphate buffer (epoetin alfa-P).

METHODS

Study subjects

Men and women 18 years of age and older who were receiving hemodialysis or CAPD were eligible for study entry. Approximately 50% of enrolled patients were to be on hemodialysis and approximately 50% were to be on CAPD. The study participants were required to have received rhEPO via subcutaneous injection for at least 3 months prior to study entry. Epoetin alfa products available to participants prior to study enrollment were citrate-buffered preparations available in single-use vials without preservative or in multi-use vials containing benzyl alcohol 0.9%, which acts as a preservative and local anesthetic. Study participants were also required to have maintained a stable hematocrit value for at least 4 weeks prior to study enrollment. At the beginning of the study, all patients were required to be receiving a dose ≥4000 IU per injection. Patients receiving hemodialysis were required to have maintained a stable vascular access for at least 4 weeks prior to starting the study. Females of childbearing potential had to use an adequate method of birth control during the study period. Written informed consent was obtained from all patients. Patients with uncontrolled hypertension (i.e. diastolic BP >100mm Hg) or a seizure disorder were not eligible for study inclusion.

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Study design

This study used a 2-period, 2-treatment crossover design, with no washout period.[12] Patients were randomly assigned to 1 of 2 treatment groups: 1) 6 consecutive subcutaneous injections of epoetin alfa-C; or 2) 6 consecutive subcutaneous injections of epoetin alfa-P. The epoetin alfa-C used in this study was manufactured by Hoffmann-La Roche, Basle, Switzerland and the epoetin alfa-P was manufactured by Cilag AG, Schaffhausen, Switzerland. Both products were distributed by Ortho Biotech, 19 Green Belt Drive, North York, Ontario, Canada. No other sources of rhEPO were permitted during the course of the study. Both preparations were clear liquids with a pH of 6.9±0.3 at 23°C±5°C. After completing 6 doses of the original therapy, the patients were switched over to a 6-dose course of the alternate therapy. Both treatments were injected in the limbs or anterior abdominal wall and the general injection site had to remain constant for each patient throughout the study. Patients on CAPD self-injected at home or were injected by their caregivers. The study medication was administered to patients on hemodialysis by the study nurses during 12 consecutive visits to the dialysis clinic. All injections were administered using a Becton Dickinson tuberculin 27-gauge needle. Dosage adjustments were permitted only if the patient's hematocrit exceeded the range deemed clinically acceptable by the investigator.

Although patients evaluated pain, redness and itching after each of the 12 injections, the primary outcome measure of interest was the patient-evaluated pain rating for the last (sixth) injection of each treatment period as measured by a visual analog scale (vas) and a verbal descriptive scale (VDS).[13] The vas is a 10cm horizontal line, without gradations, ranging from "no pain" at 0cm to "pain as bad as it could be" at 10cm. The VDS consists of 7 numbered descriptors in which 1=no pain and 7=almost unbearable pain. The patients' ratings were recorded on patient evaluation cards that also included 3 questions:

- Did you feel itchiness at the injection site after injection?;
- Did you see redness at the injection site after injection?; and
- If you felt pain at the injection site after injection, how long did it last?

At study visit 1, a physical examination (including sitting BP) was performed, and a medical and therapeutic

history was obtained from all study patients. Blood samples were obtained from each patient for an analysis of hemoglobin, hematocrit, differential white blood cell count and platelet count. Each patient on CAPD who was to self-inject or be injected by a caregiver at home was given study medication and evaluation cards on which to record the date, dose, site of injection and their evaluation of pain after each injection. At this visit, concomitant medications were recorded, and patients were trained in how to inject, observe and rate any local reaction. Each site's nurse/coordinator was responsible for teaching subjects how to score the VAS and VDS and how to answer the questions concerning redness, itchiness and duration of pain.

The second visit for patients on CAPD took place after the sixth dose of the first study medication and before the first dose of the second study medication. At this time, patients were provided with the alternate study medication and evaluation cards. The investigator recorded the occurrence of any adverse events, any changes in concomitant medications and the patient's sitting BP. The third and last evaluation visit occurred within 7 days of the final dose of the second study medication. The investigator once again recorded the occurrence of any adverse events, any changes in concomitant medications and the patient's sitting BP. A blood sample was obtained for hematological analysis.

In patients on hemodialysis, study medications were administered by a study nurse at the dialysis clinic on each of 6 consecutive visits during each of the treatment periods. Patients recorded their pain ratings on the evaluation cards, which were then collected by the study nurse. Other administrative procedures were similar to those used with patients on CAPD.

Safety outcomes were evaluated according to the hematology analysis, sitting BP, and adverse event monitoring at each visit. In addition, all investigators were requested to evaluate all adverse experiences with respect to their timing (date of onset and resolution, duration), severity (mild, marked, moderate) and relationship to the test medication (certain, probable/likely, possible, unlikely).

Statistical analysis

For purposes of power and sample size calculations, a difference between the 2 buffers of 30mm on the VAS was considered clinically significant. This decision was based on findings from 2 studies[5,11] where a difference of 20–30mm in VAS score of a citrate-buffered vehicle versus saline 0.9% resulted in a significant increase in the percentage of patients experiencing moderate to severe pain. The standard deviation was set to 40mm with α=0.05. The model used was the 2-way, 2-treatment crossover, using the central t-distribution to mimic the final analysis.[12,14,15] A level of 0.05 was considered to be statistically significant for between-buffer comparisons. The iterative procedure indicated that 22 patients would be required to yield a power of 91.7%. To adjust for possible noncompleters (10%), the sample size was initially increased to 24 patients, allowing 12 patients to be randomized to each treatment order. The sample size was then doubled to 48 patients to allow for possible subgroup analyses (e.g. self-administered, nurse/caretaker administered). However, randomization was not stratified by procedure and ultimately the data were not presented by subgroup.

Each patient was required to complete both treatment periods to be eligible for the efficacy crossover analysis. The sums and differences of the 2 treatment orders, across periods, were tested to determine the effects of period and treatment. All data were

Table I—**Patient characteristics at baseline by treatment order**

	Epoetin alfa-C First (n=24)	Epoetin alfa-P First (n=24)	All Patients (n=48)
Gender			
Female	11 (45.8%)	15 (62.5%)	26 (54.2%)
Male	13 (54.2%)	9 (37.5%)	22 (45.8%)
Age (yrs; mean ± SD)	53.4 ± 14.6	48.4 ± 16.7	50.9 ± 15.8
Race			
Caucasian	20 (83.3%)	19 (79.2%)	39 (81.3%)
Other	4 (16.7%)	5 (20.8%)	9 (18.7%)
Weight (kg; mean ± SD)	71.4 ± 15.3	67.8 ± 13.4	69.5 ± 14.4
Systolic BP (mm Hg; mean ± SD)	136.3 ± 17.3	143.3 ± 26.6	139.8 ± 22.5
Diastolic BP (mm Hg; mean ± SD)	74.2 ± 14.2	78.9 ± 14.1	76.5 ± 14.2
Hematocrit (mean ± SD)	0.312 ± 0.047	0.314 ± 0.051	0.313 ± 0.048
Hemoglobin (g/L; mean ± SD)	105.8 ± 14.9	105.0 ± 17.2	105.4 ± 15.9
Disease duration (months; mean ± SD)	116.7 ± 92.7	110.7 ± 108.9	113.5 ± 100.4
Type of dialysis			
Hemodialysis	18 (75.0%)	14 (58.3%)	32 (66.7%)
CAPD	6 (25.0%)	10 (41.7%)	16 (33.3%)
Dose – 4000U/mL	20 (83.3%)	19 (79.2%)	39 (81.3%)
Volume – 1.0mL	20 (83.3%)	21 (87.5%)	41 (85.4%)
Gauge of needle prior to study – 25	18 (75.0%)	15 (62.5%)	33 (68.8%)
Frequency of administration			
Once weekly	1 (4.2%)	1 (4.2%)	2 (4.2%)
Twice weekly	13 (54.2%)	12 (50.0%)	25 (52.1%)
Thrice weekly	10 (41.7%)	11 (45.8%)	21 (43.8%)

summarized, with all possible patient data, including the last-observation-carried-forward dataset. This dataset uses the last observation/assessment value for all missing assessments at future time points for patients who do not complete all evaluations..

The Wilcoxon signed rank test was used for comparison of the VAS and the VDS evaluations. Additional analyses included the pain ratings for days 1 through 5, and 3 calculated outcomes: 1) the mean of all available responses, regardless of the number of available responses; 2) the mean of the responses only where all 6 pain ratings were available ("mean of 6"); and 3) the last available pain rating (LAV). For pain duration, the mean of available responses, the mean of all 6 responses and the last available response were also analyzed. Pain ratings and pain duration were also analyzed using repeated measures analysis of variance for a 2-period crossover design, which provides a test for carryover, for between buffers and for between periods.[12,14] The test for carryover was performed because one of the assumptions of the crossover study design is that the effects of the first treatment must not carry over into the second treatment period.[12,14] These may be physical or psychological effects. Any such carryover could then affect the analysis of outcome measures and possibly confound the interpretation of the results. However, the test for carryover is not considered to be very sensitive.[12] Therefore, the test is considered statistically significant at the $p \leq 0.10$ level.[12]

For redness and itchiness, the buffers were compared using McNemar's chi-square test.[15] Any occurrence, when all 6 evaluations were available, and the last occurrence, were examined.

Adverse events were reviewed for treatment or time-dependent trends. All patients who met the entry criteria and received at least one dose of study medication were included in the safety analysis. Where warranted, the chi-square or Fisher's exact test were used to compare the incidence of adverse events (preferred terms). Blood pressure and hematological outcomes were analyzed using repeated measures analysis of variance for a 2-period crossover design.[12]

RESULTS

Patient demographics

Table I displays the demographics and dialysis-related information for each of the 2 treatment groups and for the study population as a whole. A total of 48 patients participated in the study, 24 of whom were randomized to treatment with epoetin alfa-C first, and 24 who were randomized to treatment with epoetin alfa-P first. Overall, the demographic characteristics of the 2 patient groups were comparable. The mean time from the first dialysis to the first study visit was 57.5 months in the epoetin alfa-C first group, and 47.9 months in the epoetin alfa-P first group. Prior to study entry, the majority of patients were receiving rhEPO alfa at a dose of 4000 IU/mL in an injection volume of 1mL using a 25-gauge needle.

A total of 13 (27.1%) patients were not included in the primary efficacy analysis. One patient took the medication out of order, and the other 12 patients did not take all 12 scheduled doses of study medication.

Efficacy outcomes

Table II shows the differences between the 2 treatments according to the responses used for within-patient comparisons based on VDS data. As illustrated, the pain ratings with the phosphate buffer formulation were consistently lower than those with the citrate buffer preparation. The differences were statistically significant on all measures. However, further analysis detected significant carryover effects in 2 comparisons (the day 6 evaluations and the "mean of 6" measure).

The pain ratings based on the VAS exhibited a similar overall pattern in that the pain ratings were consistently lower with the phosphate buffer as compared with the citrate buffer (Table III). Again, the differences were statistically significant on each measure. Further analysis detected significant carryover effects in several comparisons (the days 1, 5 and 6 evaluations, and the "mean of 6" measure).

Other efficacy outcomes included assessments of pain duration, as well as redness and itching at the injection site. As shown in Table IV, the duration of pain was significantly

Table II—**Verbal Descriptor Pain Scale⁺ (VDS) ratings (mean ± SD) for those responses used for within-patient comparison of citrate and phosphate buffer preparations**

Evaluation	n	Epoetin-alfa-C Rating	Epoetin alfa-P Rating	Difference Mean ± SD	p value
Day 1	44	2.95 ± 1.70	1.82 ± 1.21	1.14 ± 1.79	<0.001
Day 2	43	2.86 ± 1.55	1.81 ± 1.38	1.05 ± 1.48	<0.001
Day 3	42	3.07 ± 1.55	1.67 ± 1.24	1.40 ± 1.29	<0.001
Day 4	40	2.73 ± 1.55	1.85 ± 1.14	0.88 ± 1.30	<0.001
Day 5	37	2.78 ± 1.49	1.81 ± 1.27	0.97 ± 1.17	<0.001
Day 6	35	2.43 ± 1.63	1.77 ± 1.24	0.66 ± 1.75	0.034
Mean[1]	44	2.82 ± 1.39	1.83 ± 0.97	0.99 ± 0.90	<0.001
Mean of 6[2]	34	2.70 ± 1.31	1.72 ± 0.96	0.99 ± 0.85	<0.001
Last available[3]	44	2.66 ± 1.70	1.86 ± 1.27	0.80 ± 1.65	0.003

⁺Visual Descriptive Scale: 1 (no pain), 2 (very mild pain), 3 (mild pain), 4 (not very severe pain), 5 (quite severe pain), 6 (very severe pain), 7 (almost unbearable pain)

[1] Mean of all available responses
[2] Mean of responses from those patients who completed all six scheduled injections
[3] Mean of the last available responses

NOTE: The pain rating differences between buffers on day 6 and between the "mean of 6" measure showed significant ($p \leq 0.10$) carryover effects.

Table III—**Visual Analog Pain Scale+ (VAS) ratings (mean ± SD) for those responses used for within-patient comparison of citrate and phosphate buffer preparations**

Evaluation	n	Epoetin-alfa-C Rating	Epoetin alfa-P Rating	Difference Mean ± SD	p value
Day 1	43	2.98 ± 3.09	1.31 ± 2.01	1.67 ± 2.89	<0.001
Day 2	43	2.59 ± 2.86	1.27 ± 2.33	1.31 ± 2.57	0.001
Day 3	41	2.96 ± 2.91	0.93 ± 1.91	2.03 ± 2.27	<0.001
Day 4	39	2.31 ± 2.69	1.30 ± 2.18	1.01 ± 1.69	<0.001
Day 5	36	2.20 ± 2.50	1.21 ± 2.03	0.99 ± 1.79	0.003
Day 6	35	2.25 ± 3.15	1.08 ± 1.95	1.17 ± 2.8	0.023
Mean[1]	44	2.57 ± 2.51	1.22 ± 1.70	1.35 ± 1.49	<0.001
Mean of 6[2]	33	2.38 ± 2.33	1.10 ± 1.70	1.27 ± 1.33	<0.001
Last available[3]	44	2.64 ± 3.24	1.20 ± 2.18	1.43 ± 2.86	0.002

+Visual Descriptive Scale: 1 (no pain), 2 (very mild pain), 3 (mild pain), 4 (not very severe pain), 5 (quite severe pain), 6 (very severe pain), 7 (almost unbearable pain)

[1] Mean of all available responses
[2] Mean of responses from those patients who completed all six scheduled injections
[3] Mean of the last available responses

NOTE: The pain rating differences between buffers on days 1, and 6, and between the "mean of 6" measure showed significant ($p \leq 0.10$) carryover effects.

shorter at every evaluation (i.e. days 1–6), as well as in each of the 3 calculated measures, with the phosphate buffer preparation. For example, the mean of all pain duration evaluations was 40.7±72.7 seconds with the citrate buffer and 6.2±10.5 seconds with the phosphate buffer. There were few reports of redness and itchiness at the injection site with either formulation. Although there was a trend toward less injection site redness and itchiness with the phosphate buffer, the differences between buffers were not statistically significant.

SAFETY

Evaluation of between-buffer differences in terms of safety was based on changes in systolic and diastolic BP and specified laboratory parameters (hemoglobin, hematocrit, platelet count, differential white blood cell count). There were no significant differences between buffer formulations in any of these parameters.

Five adverse events were reported by patients while receiving the phosphate buffer formulation and 3 adverse events were reported by patients while receiving the citrate buffer formulation. All events were considered to be unrelated to the study medications. No patients were discontinued from the study due to an adverse event.

DISCUSSION

The present randomized, double-blind, crossover study was performed to test the hypothesis that rhEPO alfa formulated with sodium phosphate as the buffer would produce less injection site discomfort than the currently available preparation of rhEPO alfa which uses a citrate buffer. The primary outcome of interest was patient-evaluated pain as assessed by 2 measures: the VDS and the VAS. The results of these assessments indicated that the phosphate-containing formulation caused significantly less injection-site discomfort than did the citrate-containing formulation although neither formulation caused as much patient-assessed pain as has been reported by other authors.[5,11] The original hypothesis that there would be a 30mm difference in VAS scores between epoetin alpha-P and epoetin alpha-C was not realized likely because the hypothesis was based on results comparing a citrate buffer with saline 0.9%.[5,11] Although the within-patient comparisons of these 2 preparations were highly significant, additional analysis detected significant ($p \leq 0.10$) carryover effects in some specific comparisons of the VDS and VAS results. Therefore, comparisons where a carryover effect is detected should be interpreted cautiously.

There are several possible reasons for such a carryover effect in the between-buffer comparisons in this crossover study. One contributing factor may have been that all patients did not complete the protocol-specified number of injections, thereby affecting the number of patients who completed both treatments. Another possible reason could be that the primary outcomes were based on patient-evaluated and recorded assessments and the patients could not be blinded to the time of crossover. As a result, there could have been a psychological carryover effect. The patients' responses could have been biased, especially for the

Table IV—**Mean (± SD) for those responses used for within-patient comparison of citrate and phosphate buffer preparations**

Evaluation	n	Epoetin-alfa-C Rating	Epoetin alfa-P Rating	Difference Mean ± SD	p value
Day 1	36	37.1 ± 62.7	3.9 ± 6.3	33.2 ± 61.6	0.003
Day 2	41	39.5 ± 78.4	4.1 ± 12.0	35.3 ± 77.6	0.006
Day 3	37	80.9 ± 203.8	2.5 ± 7.6	78.4 ± 204.3	0.019
Day 4	35	33.6 ± 64.1	9.1 ± 27.5	24.5 ± 64.6	0.038
Day 5	30	30.2 ± 55.3	6.2 ± 12.5	24.1 ± 55.1	0.024
Day 6	32	27.1 ± 65.1	4.9 ± 10.1	22.2 ± 66.9	0.037
Mean[1]	44	40.7 ± 72.7	6.2 ± 10.5	34.5 ± 70.3	0.029
Mean of 6[2]	23	37.1 ± 73.9	3.7 ± 7.9	33.3 ± 74.6	0.010
Last available[3]	44	34.6 ± 72.2	4.8 ± 9.6	29.8 ± 73.0	0.002

[1] Mean of all available responses
[2] Mean of responses from those patients who completed all six scheduled injections
[3] Mean of the last available responses

VDS, by their recall of their previous responses. Finally, a carryover effect may have been due to chance.

However, there was a significant difference in favour of the phosphate buffer in terms of duration of pain, and a trend for the phosphate buffer to induce less redness and itchiness at the injection site. As would be expected, there was no evidence that the 2 buffers differed in terms of safety.

In conclusion, the results of this randomized, double-blind, crossover study indicate that the epoetin alfa formulation using sodium phosphate buffer is associated with less injection-site discomfort and a shorter duration of pain than the formulation containing a citrate buffer. Although the between-buffer tests were statistically significant for the key outcome measures, evidence of a carryover effect allows us to conclude only that there is a trend toward less pain with the phosphate buffer. Therefore, an epoetin alfa formulation using sodium phosphate as the buffer may provide an advantage in local tolerability and compliance.

These findings are consistent with other reports in the literature.[5,11] Furthermore, the phosphate-buffered product is now available in Canada in ready-to-inject, pre-filled syringes which have been designed to facilitate patient injection, as well as to attenuate injection discomfort.

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