

Coadministration of Lidocaine and Recombinant Human Erythropoietin-Beta: Effect on Pain and of Erythropoietin Pharmacokinetics

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ABSTRACT

Background: Subcutaneous injections of recombinant human erythropoietin is associated with significant pain at the injection site. The present study evaluated whether lidocaine reduces the pain associated with subcutaneous injection of recombinant human erythropoietin-beta (rhEPO- β) and whether coadministration of lidocaine alters the pharmacokinetics of erythropoietin.

Methods: Fifteen hundred units of rhEPO- β (Epopgen) or a combination of 1500 units of rhEPO- β and 0.1 mL of 1% lidocaine (Xylocaine) were administered subcutaneously to 4 study subjects. After injec-

tions, pain reduction was assessed using visual analog scale (VAS). Blood samples were collected at designated intervals to measure serum erythropoietin (EPO) concentrations. The pharmacokinetic parameters such as area under the serum concentration-time curve (AUC_{0-48}), peak concentration (C_{max}), time to the C_{max} (t_{max}), and terminal elimination half-life ($t_{1/2}$) were calculated by the usual methods.

Results: The values of VAS were 8.3 ± 2.3 and 1.7 ± 1.2 for rhEPO- β alone and the combination with lidocaine, respectively, indicating that injection pain caused by rhEPO- β was reduced by the coadministration of lidocaine. The value of AUC_{0-48} was 471.2 ± 176.7 (mean \pm SD) mIU.mL/h for rhEPO- β and 675.1 ± 292.0 mIU.mL/h for the combination; the value of C_{max} was 15.3 ± 3.7 mIU/mL for rhEPO- β and 24.2 ± 8.8 mIU/mL for the combination. The value of t_{max} was 27.75 ± 23.41 h and 10.50 ± 3.87 h

for the combination, and the $t_{1/2}$ value was 17.91 ± 0.30 h for rhEPO- \square and 37.10 ± 10.32 h for the combination. However, no significant differences in the pharmacokinetic parameters of EPO were observed between rhEPO- \square injection with or without lidocaine.

Conclusion: No significant differences in the bioavailability parameters were observed between rhEPO- \square alone and the combination of rhEPO- \square and lidocaine.

Coadministration of lidocaine seems to be effective for pain caused by subcutaneous injection of rhEPO- \square without causing any problems in clinical safety.

INTRODUCTION

The subcutaneous administration of recombinant human erythropoietin beta (rhEPO- \square) is generally used in patients undergoing chronic ambulatory peritoneal dialysis (CAPD) and pre-dialysis in end stage renal disease. Treatment of renal anemia results in increased life expectancy and improved quality of life for patients.^{1,2} On the other hand, the injection pain produced by subcutaneous injection of rhEPO- \square is a significant problem for patients receiving repeated treatments. Therefore, numerous investigators have examined the differences in pain associated with a using a variety of drug preparations^{1,3-6} the influence of the dissolution medicines on pain,^{7,8} and alleviation of pain using local anesthetics.^{9,10} However, these investigators have not been concerned with rhEPO- \square which is widely used in Japan. Moreover, there are no reports concerning the pharmacokinetics of erythropoietin (EPO) after rhEPO- \square was coadministered with local anesthetics. Therefore, we investigated the effect of lidocaine on the pain produced by subcutaneous injection of rhEPO- \square and on the pharmacokinetics of EPO in healthy male subjects. The possibility of clinical use of this combined therapy is also discussed.

METHODS

Subjects

Four male volunteers (age range, 27 to 36 years; weight range, 60 to 80 kg; height range, 164 to 174 cm) participated in this study, after giving written informed consent. The results of clinical examination and laboratory tests showed the subjects were in good health. None of the subjects were on medication.

Medications

Recombinant human erythropoietin beta (rhEPO- \square) for subcutaneous injection (EPOGEN) was obtained from Chugai Pharmaceutical Company (Tokyo, Japan). The injection contains 1,500 IU of rhEPO- \square dissolved in a 0.5 mL solvent (pH 5.5 to 6.5) containing *L*-histidine hydrochloride and polysorbate 80 (information from manufacturer). Xylocaine (AstraZeneca Co., Osaka, Japan) brand lidocaine was used, which contains 1% of lidocaine hydrochloride.

Study Design

This investigation was composed of 2 separate studies. In both studies, a randomized, double-blind, crossover study was used with intervals of 1 week as a washout period. The subjects received subcutaneous injection of 1,500 IU of rhEPO- \square alone or as a co-injection with 0.1 mL of 1% lidocaine. The injection site was cleansed using a 70% alcohol solution and a 25-gauge needle was used to minimize the injection pain.

The pain at the injection site was assessed using a visual analog scale (VAS) with the method reported previously by Machin and colleagues.¹¹ Briefly, the subjects were asked to score the level of pain on a scale of 1 to 10 (0 indicating no pain at all and 10 indicating the worst pain) on a 10-cm chart immediately after subcutaneous injection of rhEPO- \square alone or rhEPO- \square plus lidocaine. To measure concentrations of erythropoietin (EPO) in serum and to investigate

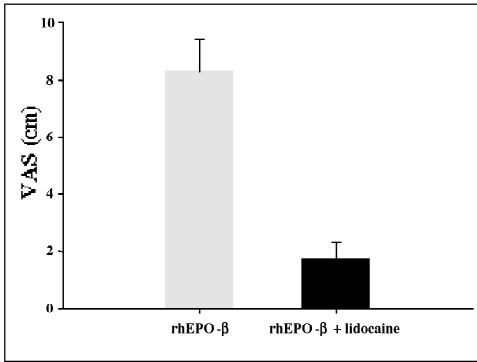


Figure 1. VAS in subjects after subcutaneous injection of EPO-β alone and EPO-β with lidocaine. Each column represents the mean ± S.E. (n = 4). Significant difference in the VAS was observed between EPO-β alone and EPO-β with lidocaine ($P < 0.0002$).

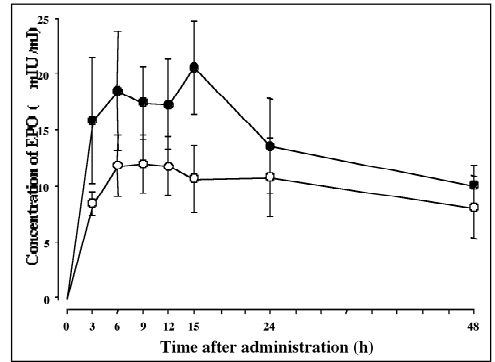


Figure 2. Serum concentration-time data for EPO after subcutaneous injection of EPO-β alone (●) and EPO-β with lidocaine (○). Each point represents the mean ± S.E. (n = 4). No significant difference was observed between EPO-β alone and EPO-β with lidocaine.

to investigate whether the addition of lidocaine influences the pharmacokinetics of EPO, blood samples were collected at designated intervals (just before, 3, 6, 9, 12, 15, 24, and 48 h after injection). Serum samples were obtained by centrifuging the blood (samples were frozen at -30°C until analysis).

Drug Analysis

Concentrations of EPO in serum were determined by radioimmunoassay according to the method reported previously.¹² Coefficient of variation for this assay was less than 10%.

Data Analysis

The concentration of EPO at each sampling point after injection minus the concentration of EPO before injection was represented as the true concentration. The pharmacokinetics of EPO was represented by the peak concentration (C_{max}) in serum, time to peak concentration (t_{max}), elimination half-life ($t_{1/2}$), and areas under the serum concentration-time curve up to 48 hours (AUC_{0-48}). The elimination rate constant (k_e) was calculated by a linear regression analysis of the log-linear phase of the serum drug concentration-time curve. The $t_{1/2}$ was calculated as $t_{1/2} = 0.693/k_e$. Area under the serum concentration-time curve, from zero to 48 hours ($\text{AUC}_{0-48 \text{ h}}$), was calculated by the linear trapezoidal rule.

Statistics Analysis

All data are expressed as mean values ± SEM. Data were analyzed by the Student t -test for paired values. Differences were regarded as statistically significant when P values were < 0.05 .

RESULTS

Adverse effects by the injection of rhEPO-β with and without lidocaine were monitored at each blood sampling time and 1 week after completing the study. No adverse events were observed.

Figure 1 shows the VAS determined after subcutaneous injection of rhEPO-β with or without lidocaine. As shown in Figure 1, the value of VAS after subcutaneous injection of rhEPO-β plus lidocaine was significantly decreased compared with that after subcutaneous injection of rhEPO-β alone (1.7 ± 1.2 and 8.3 ± 2.3 cm, respectively).

No significant differences in the serum concentrations of EPO at each sampling point were observed between rhEPO-β alone and rhEPO-β plus lidocaine (Figure 2). The corresponding pharmacokinetic parameters of $\text{AUC}_{0-48 \text{ h}}$, C_{max} , t_{max} and $t_{1/2}$ of EPO are summarized in Table 1. There were no significant differences in any parameters between the two treatments, although the addition of lidocaine had a tendency to increase $\text{AUC}_{0-48 \text{ h}}$, C_{max} , and $t_{1/2}$.

Table 1. Pharmacokinetic Parameters of EPO After Subcutaneous Injection of rhEPO- α With or Without Lidocaine

Parameter	rhEPO- α	rhEPO- α with lidocaine
C _{max} (mIU/mL)	15.3 \pm 1.8	24.2 \pm 4.4
t _{max} (h)	27.8 \pm 11.7	10.5 \pm 1.9
t _{1/2} (h)	17.9 \pm 0.2	37.1 \pm 5.2
AUC _{0-48 h} (mIU h/mL)	471.2 \pm 88.4	675.1 \pm 146.0

Each value represents mean \pm standard error (n = 4).
There were no significant differences between rhEPO- α and rhEPO- α with lidocaine.

DISCUSSION

Recombinant human erythropoietin (rhEPO) is one of the few anemia treatments for patients with end stage renal failure. The additives for the solution stability of rhEPO- α include weak acid, which contribute to pain at the subcutaneous injection site. In the present study, we investigated whether lidocaine alleviates the pain produced by subcutaneous injection of rhEPO- α and modifies the pharmacokinetics of erythropoietin.

Subcutaneous injection of rhEPO- α is generally used for patients with CAPD and patients undergoing pre-dialysis at the end stage of renal failure, and has a remarkable effect on prognosis and quality of life.^{13, 14} Moreover, rhEPO is readily available and its utility is expected to increase in the future.¹⁵ On the other hand, injection pain is an important problem for patients receiving repeated treatment with rhEPO- α .¹ The degree of pain caused by subcutaneous injection of rhEPO- β varies depending on variations in preparations.^{1, 4-8} The local pain associated with the subcutaneous injection is often described as burning, itching, or stinging.^{5, 10, 13} We investigated whether coadministration of lidocaine can improve injection pain caused by subcutaneous injection of rhEPO- α and whether lidocaine affects the pharmacokinetics of EPO. We chose the rhEPO- α formulation because the syringe-type injection is often used clinically and there is little information regarding injection pain with rhEPO- α , although there are many reports about pain with rhEPO-

α .¹⁶⁻¹⁸ In the present study, 0.1 mL of 1% lidocaine was used as a local anesthetic because the use of 0.2 mL of 2% lidocaine has been reported to reduce injection pain.⁸

The present study found that coadministration of lidocaine significantly attenuated the injection pain caused by subcutaneous injection of rhEPO- α compared with that by rhEPO- α alone (Figure 1), probably due to the local anesthetic action of lidocaine. The results obtained in this study were consistent with the results of previous studies,^{8, 9} which co-administered 0.2 mL of 2% lidocaine with rhEPO- α . Differences in lidocaine dosages between other studies and ours may be explained by variations in body weight between foreign and Japanese subjects. These results suggest that the dosage of lidocaine used in this study is enough to reduce the injection pain by subcutaneous injection of rhEPO- α for Japanese patients.

In the present study, coadministration of lidocaine did not change significantly the pharmacokinetics and serum concentration-time curve of EPO, suggesting that the combined therapy of rhEPO- α and lidocaine is able to attain the same effect as therapy with rhEPO- α alone. Interestingly, peak concentration of EPO obtained after coadministration of rhEPO- α with 0.1 mL of 1% lidocaine tended to be higher than that by rhEPO- α alone. These results suggest that coadministration of lidocaine increased the absorption of rhEPO- α , although the cause remains unclear. If the coadministration of 1% lidocaine could improve the absorption of rhEPO- α , it is expected to reduce the

dosage of rhEPO- α , which might result in cost savings. Based on these findings, it is expected that the decrease in pain from coadministration of rhEPO- α with lidocaine might improve the quality of life for patients undergoing treatment.

In conclusion, the results of the present study suggest that coadministration of rhEPO- α with lidocaine can be expected to have the same efficacy as rhEPO- α alone, without any side effects, and is an effectively combined therapy for the alleviation of the injection pain by rhEPO- α . Since the number of subjects that participated in this study was small, further studies with more subjects are necessary to confirm the results and evaluate the long-term safety and efficiency of this combined therapy.

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