—Regular Articles—

Fluctuation in Therapeutic Control Associated with Interchange of Prednisolone Tablet Formulations: Assessment of Bioequivalence by Dissolution Test

Hiroki KONISHI,*[,a] Kashie KANEMOTO,[a] Yoshihiro IKUNO,[a]
Tokuzo MINOUCHI,[a] Tetsuya INOUE,[b] Keiko HODOHARA,[c]
Yoshihide FUJIYAMA,[b] and Akira YAMAJI[a]

Department of Hospital Pharmacy,[a] Second Department of Internal Medicine,[b] and Department of Hematology[c] of Shiga University of Medical Science, Seta, Otsu 520–2192, Japan

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A 47-year-old woman received combination therapy with prednisolone (PSL), danazol, cepharanthin, ascorbic acid, and cimetidine for the treatment of idiopathic thrombocytopenic purpura. The platelet count was well controlled for over 1 year. Then the PSL tablet formulation was altered from Tablet A to Tablet B with the same treatment regimen, but the platelet counts fell drastically thereafter. However, the platelet counts recovered by changing the PSL tablet formulation back from Tablet B to Tablet A. *In vitro* dissolution testing was undertaken to assess bioequivalence between Tablet A and Tablet B. PSL in Tablet B was released more slowly compared with that in Tablet A regardless of the medium pH conditions, and the difference in the release rate between the two tablet formulations increased with increasing medium pH value. The difference exceeded the allowance limit (15%) for judgement of bioequivalence under conditions above pH 4, indicating that Tablet A and Tablet B might be nonbioequivalent. The intragastric pH of the patient was probably raised due to coadministration of cimetidine. Therefore the present results suggest that the disparity in the immunosuppressive effects between the two PSL tablet formulations was attributable to the difference in their dissolution behavior in the gastrointestinal tract. We consider that it is better to avoid interchanging PSL tablet formulations in clinical practice.

Key words——prednisolone tablet formulation; dissolution test; bioequivalence; idiopathic thrombocytopenic purpura; platelet count

INTRODUCTION

Prednisolone (PSL), a synthetic glucocorticosteroid, is commonly used to treat a variety of immunologic, allergic, and inflammatory diseases. In Japan, as in other countries, a number of pharmaceutical companies market their original PSL formulations based on extensive clinical demand and the management strategy for stable profit, although the end price of the pharmaceutical products is regulated by the health insurance system. The Ministry of Health, Labor and Welfare requires that each PSL formulation be manufactured to meet the quality assurance requirements specified in the Japanese Pharmacopoeia (JP),[1] but it has not been confirmed whether the efficacy and safety are equivalent among the PSL formulations. In recent clinical reports on treatment with levothyroxine,[2] valproic acid,[3] clozapine,[4,5] and warfarin,[6] it was pointed out that there was significant disparity in the therapeutic outcome between tablet formulations, although the quantity of active ingredients and dosage form were identical. This is attributed to the lack of bioequivalence between the tablet formulations because vehicles and manufacturing processes may differ.

In this paper, we present a case of fluctuating immunosuppressive control in a patient after interchanging two brand-name PSL tablet formulations and examine the release characteristics of PSL from the two PSL tablet formulations by *in vitro* dissolution testing to discuss this clinical event.

MATERIALS AND METHODS

Standard PSL was purchased from Sigma Chemical (St. Louis, MO, USA). PSL tablet formulations (Tablet A [lot no. 0053] and Tablet B [lot no. 0330], 5 mg/T) were obtained from Shionogi & Co. (Osaka, Japan) and Takeda Chemical Industries (Osaka, Japan), respectively. All other chemicals and solvents were of analytical grade.

e-mail: konishi@belle.shiga-med.ac.jp

The dissolution test was carried out at 37±0.5°C in accordance with the specifications in the Japanese Pharmacopoeia, 14th edition (JP XIV), using round-bottomed glass chambers attached to a rotation paddle apparatus (Model PTW-II, Pharm Test). The test media used in this study were JP XIV reference fluid (distilled water), JP XIV first fluid (pH 1.2), 0.05 M acetate buffer (pH 4.0), 0.1 M phosphate buffer (pH 6.0), and JP XIV second fluid (pH 6.8). The medium volume was 900 ml, and stirring speed was set at 50 rpm. The amount of PSL released into the test medium from the tablets was determined by successive monitoring of absorbance at 248 nm by using a flow-through cell system (Model UV-1200 spectrophotometer, Shimadzu) after passing the solution through a fine glass filter (F-72, Toyama Sangyo). Aqueous solution of PSL (5.56 μg/ml [5 mg/900 ml]) was used as a standard. Measurements were repeated 18 times under the same conditions, and the release rate was defined as the mean of their determinations. The validity of the adopted spectrophotometric method for the dissolution test was confirmed by HPLC analysis.[7)]

RESULTS

Case Presentation The patient was a 47-year-old woman (weight 53 kg, height 157 cm), who did not smoke and drink alcohol, who had been diagnosed with idiopathic thrombocytopenic purpura (ITP) and systemic lupus erythematosus (SLE) 18 years previously. She received pulse therapy with steroid and cyclophosphamide, γ-globulin injection, and platelet transfusion when ITP worsened. After remission she was being treated with only oral drugs during outpatient follow-up at the Hospital of Shiga University of Medical Science. The platelet count was maintained at the level above 20×10^3/mm^3 during concomitant treatment with PSL (25 mg/day, Tablet A [5 mg/T]), danazol (100 mg/day), cepharanthin (60 mg/day), ascorbic acid (1.5 g/day), and cimetidine (800 mg/day) for over 1 year. PSL was administered once daily in the morning. The daily PSL dose was tentatively reduced to an average 22.5 mg/day (alternate administrations of 25 mg/day and 20 mg/day), but a significant decrease in platelet count was observed thereafter. The dosage was returned to 25 mg/day, and the platelet counts recovered.

On February 20, 2001, the patient visited another hospital for outpatient consultation with a referral from our hospital, due to her stable disease. The same treatment regimen was continued, although another PSL tablet (Tablet B [5 mg/T]) was prescribed instead of Tablet A. On March 27, 2001, the patient consulted our hospital because of severe general fatigue with increased purpura and gum bleeding. As the platelet counts at that time were found to have drastically fallen to 3×10^3/mm^3, she was hospitalized immediately. Compliance with the prescribed treatment regimen was unfailing according to the patient. No signs of recurrence of SLE were indicated by clinical laboratory tests. On admission, Tablet A was prescribed in place of Tablet B, although the treatment regimen was unchanged. Following the change from Tablet B to Tablet A, the platelet count increased to the original level after about 1 week, and the bleeding improved markedly. She was discharged on April 8 because the serious symptoms had resolved, and the platelet count was well controlled thereafter. Figure 1 shows the changes in platelet count in the patient from January 2000.

Dissolution Test The dissolution profile of PSL from Tablet A and Tablet B is shown in Fig. 2. Both tablets were apparently disintegrated and dissolved within 50 min, and at least 85% of labeled PSL was released within 15 min from Tablet A. However, PSL of Tablet B was released more slowly than that in Tablet A, irrespective of the medium conditions. Figure 3 shows the difference in the release rate of PSL between Tablet A and Tablet B when 85% of the PSL in Tablet A had been released. The difference increased with the increase in pH value of the medium, and the disparity exceeded 15% under medium conditions above pH 4.

DISCUSSION

ITP is an immunoregulatory disorder characterized by platelet destruction associated with an overproduction of specific autoantibody that augments platelet phagocytosis in the reticuloendothelial system. PSL is recommended as the first-choice immunosuppressant for maintenance of platelet function in patients with chronic ITP. In the present case, a remarkable worsening of ITP (continuous bleeding due to platelet count reduction) occurred after changing from Tablet A to Tablet B, and then a pronounced improvement of the ITP symptoms with recovery of platelet count was observed only after changing from Tablet B back to Tablet A, although all other medica-

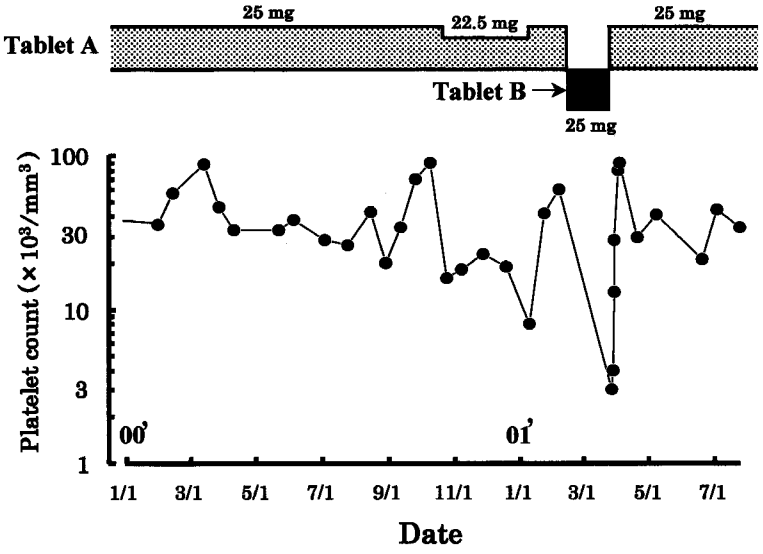

Fig. 1. Change in Platelet Count in the Patient with Change in PSL Tablet Formulations

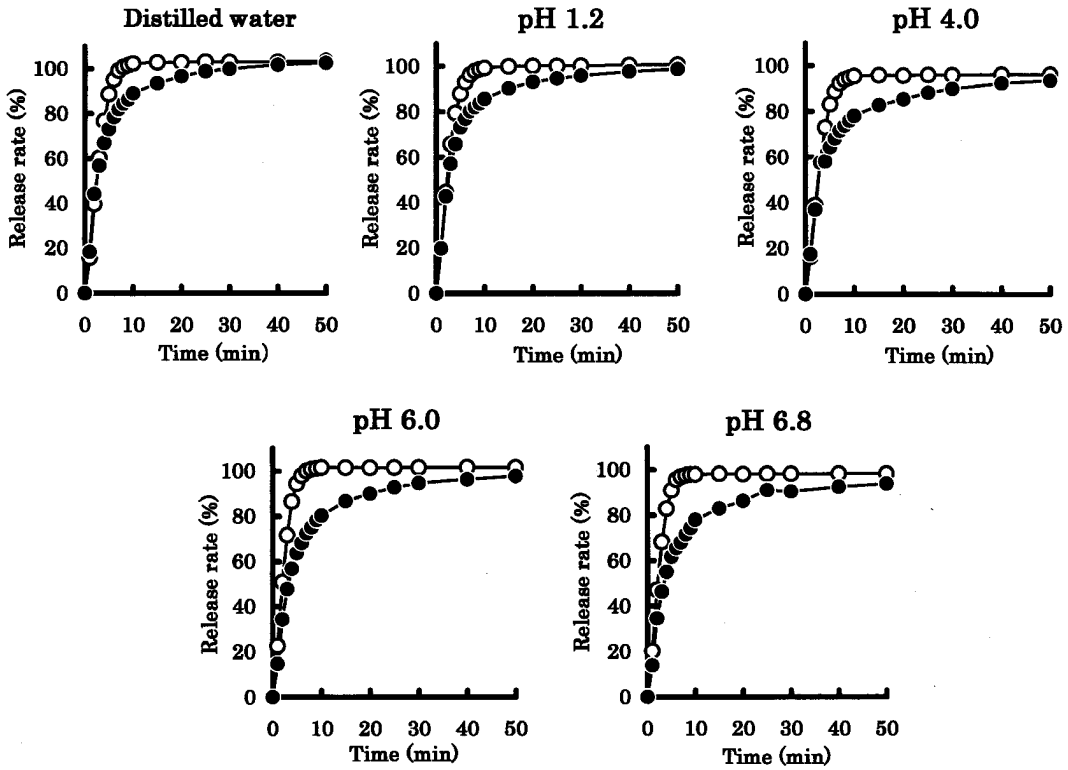

Fig. 2. Dissolution Test of the Two PSL Tablet Formulations
Symbols, ○: Tablet A, ●; Tablet B.

tions remained unchanged. The application of Naranjo's algorithm[8] indicated a probable association between fluctuation in the therapeutic response and interchange of PSL formulations, although rechallenge with Tablet B was not attempted. In previous reports, therapeutic failure after prescribing another formulation of prednisone, a prodrug of PSL, was demonstrated, and it was confirmed that such cases were attributed to differences in dissolution profiles among the prednisone tablet formulations.[9—11]

As shown by the dissolution test in the present study, the release rate of PSL in Tablet B was lower

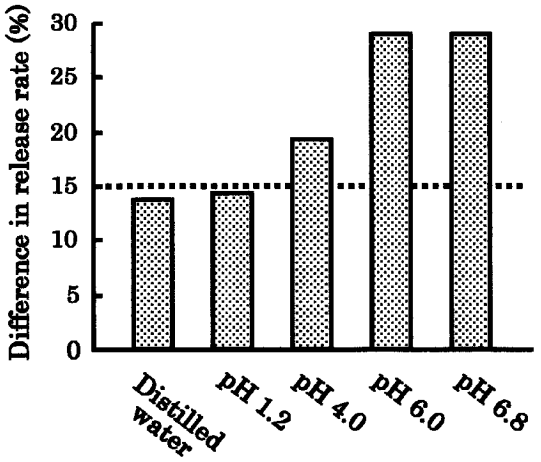

Fig. 3. pH-Dependency of Difference in PSL Release between Tablet A and Tablet B

The release rate of PSL from Tablet B was calculated at the time when 85% of the PSL was released in Tablet A. Each column shows subtraction of the release rate of Tablet B from the release rate (85%) of Tablet A under the various medium conditions. Dotted line represents allowance limit (15 %) for judgment of bioequivalence.

than that in Tablet A (Fig. 2). This result was compatible with the clinical observations described above. As previous *in vitro/in vivo* correlation studies employing healthy subjects indicated that the rank orders of the dissolution rate of immediate-release PSL tablets were similar to those of the gastrointestinal absorption rate,[12,13] PSL in Tablet B was likely to be absorbed more slowly as compared with that in Tablet A. Based on the authorized guidance of the dissolution test,[14] it can be interpreted that there is a high possibility of nonbioequivalence between the two products if not less than a 15% difference in the release rate is observed at the time when approximately 85% is released from one product. PSL was released from the tablets in a pH-dependent manner, and the extent of difference in the release rate of Tablet A and Tablet B was outside the allowance limit (15%) for the judgment of bioequivalence[14] under the medium conditions above pH 4 (Fig. 3). This suggests that Tablet A and Tablet B might be nonbioequivalent. The present patient was coadministered the H_2-receptor antagonist cimetidine at a daily dose of 800 mg for prevention of peptic ulcer caused by PSL, and it was suspected that the intragastric pH value was elevated above pH 5 due to depression of acid secretory function.[15,16] Therefore this physiological status might affect the absolute bioavailability of PSL in Tablet B in connection with the further delay in the absorption rate.

The international criteria for the decision on *in vivo* bioequivalence between the test and reference products is that the 90% confidence interval for the ratios of the geometric mean AUC and Cmax values falls within 80—125%.[17] According to this acceptance criteria, a 20% difference in AUC and Cmax between two products is acceptable even if they are judged to be bioequivalent. Our patient once experienced a decrease in platelet counts after a 10% dose reduction in PSL from 25 mg/day to 22.5 mg/day. That episode suggests that she is highly susceptible to modification of PSL dosage even though the dose adjustment is within the acceptable range of bioequivalence, and it provides strong support for the significant difference in the therapeutic response to the two PSL formulations.

The Japanese guidelines require the dissolution test to assess the bioequivalence of generic drugs to innovator drugs in addition to *in vivo* comparison in pharmacokinetic studies.[18] However, there is no distinction between generic and innovator products in the PSL formulations sold on the market in Japan, because PSL is a JP-listed drug that can be manufactured without restriction under patent permission. The dissolution test of PSL is thus not formally required, but the present study provided evidence that there is a significant disparity in dissolution behavior among PSL formulations, and that this difference was likely to reflect fluctuations in the clinical effect.

In conclusion, we consider that it is better to avoid interchanging PSL tablet formulations in clinical practice regardless of brand, taking its strong biological action into account.

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