Rectal Absorption of Ozagrel from a Suppository Containing Its Commercial Tablet in Healthy Human Subjects

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A suppository containing an ozagrel tablet was prepared using Witepsol H-15 as a base, and its rectal absorption was studied in human male volunteers. In comparison, a commercially available ozagrel tablet was administered orally to all the individuals in a cross-over design. After rectal dosing, ozagrel was absorbed rapidly at a \( T_{\text{max}} \) of 0.75h, and its elimination half-life was longer than after oral dosing. The extent of absorption of ozagrel after both administration routes was similar. However, the bioavailability of the rectal suppository is \( 92 \pm 37\% \) (mean \( \pm S.D.; n = 6 \)) relative to the oral tablet. The tablet-containing suppository is easy to prepare, with its content being accurate and reproducible. Thus, the present study suggests that the rectal administration of an ozagrel suppository is a practical and promising alternative to oral administration, especially for patients who cannot tolerate tablets orally. This study demonstrated for the first time the possibility of an ozagrel suppository in human subjects.

Key words ozagrel; suppository; absorption; human

Ozagrel, \((E)-3-[p-(1H-imidazole-1-ylmethyl)phenyl]-2-propenoic acid, is a selective thromboxane synthetase inhibitor.\) It is commercially available as either a tablet or solution for injection; the former is used for the treatment of bronchial asthma and the latter to improve motor disturbances after cerebral thrombosis.\(^2,3\) We have reported that ozagrel is completely absorbed after rectal administration as a suppository in rabbits.\(^4\) Based on the animal data, there have been some inquiries regarding using an ozagrel suppository in patients in our hospital. Moreover, from the viewpoint of pharmacoeconomics, the use of tablets is much more advantageous than an injectable solution (cost of 100 mg ozagrel: 1210 yen per injection and 122.8 yen per tablet). Therefore, in this study, we evaluated the pharmacokinetic benefit of the ozagrel suppository by comparing the absorption profiles of the drug after administration of its oral tablet and suppository containing a tablet in healthy human subjects.

MATERIALS AND METHODS

Materials Ozagrel hydrochloride tablets (Domenan\(^8\)) were obtained from Kissei Pharmaceutical Ind., Ltd. (Matsumoto, Japan). Witepsol H-15 was obtained from Maruishi Pharmaceutical Co., Ltd. (Osaka, Japan). Other reagents were commercially available and of analytical grade.

Preparation of Ozagrel Suppository A suppository containing an ozagrel tablet (Fig. 1) was prepared as described previously.\(^4\) Briefly, Witepsol H-15 was melted at 40—50 °C, and 1.8 ml of it was poured into a 2.25 ml plastic mold. One tablet of 100 mg ozagrel hydrochloride was then placed into the mold. After a few minutes, another 0.2 ml of the melted base was added into the mold. The suppository was cooled at room temperature.

Subjects Six healthy male Japanese, aged 24—38 years and weighing 60—72 kg, participated in this study. Each volunteer gave his informed consent before participating in the study. Prior to the study, a medical history was recorded, and biochemical and hematological tests were performed. All results were within the normal range.

Study Design All the volunteers fasted for 12 h before the medication. Each subject received 100 mg of ozagrel by oral tablet and a rectal suppository, with a one-week washout period in a cross-over design. The ozagrel tablet was taken with 100 ml of water. Food was withheld for 4 h after each dose. Before each dosing, an indwelling catheter was inserted to the forearm vein, with a heparin lock attached. After drug administration, blood (1 ml) was withdrawn at 0, 0.5, 1, 1.5, 2, 3, and 4 h for oral dosing and at 0, 0.25, 0.5, 1, 1.5, 2, and 4 h for rectal dosing. Plasma was separated by centrifugation and frozen at \(-80^\circ\text{C}\) until analysis.

Drug Assay The plasma concentrations of ozagrel were measured by a high performance liquid chromatographic (HPLC) method reported previously,\(^4\) with some modification. Briefly, 0.2 ml of plasma was added to 0.6 ml of methanol and mixed well. The mixture was centrifuged at 10000 rpm for 2 min, then the supernatant was transferred to another vessel and evaporated to dryness by a \(N_2\) gas stream. The residue was dissolved with 200 \(\mu\)l of a mobile phase, then 50 \(\mu\)l of the solution was applied to HPLC. The HPLC system consisted of a pump (LC-6AD, Shimadzu, Kyoto, Japan), a UV detector (SPD-6A, Shimadzu) and an autoinjector (SIL-9A, Shimadzu). A reversed-phase TSK-Gel ODS-80 TM column (150 x 4.6 mm i.d.; pore size 5 \(\mu\)m) (Toyoda Soda,

![Fig. 1. A Schematic Illustration of the Suppository Containing a Commercially Available Ozagrel Tablet](image-url)
Tokyo, Japan) was used. The column temperature was kept at 40 °C. The mobile phase was acetonitrile-0.01 M acetate buffer (pH 4.0) (4:96, v/v). The drug was detected at a wavelength of 274 nm and quantified by an integrator (C-R6A, Shimadzu).

**Pharmacokinetic Analysis** The model-independent pharmacokinetic parameters of half-life ($t_{1/2}$), maximum plasma concentration ($C_{\text{max}}$), peak time ($T_{\text{max}}$), mean residence time ($MRT$), and area under the plasma concentration–time curve ($AUC$) were estimated by a moment method implemented in Excel macros for each subject. The relative bioavailability ($F_{\text{rel}}$) of a suppository compared with an oral tablet was calculated by:

$$F_{\text{rel}} = \frac{AUC_{\text{rel}}}{AUC_{\text{oral}}}$$

Statistical analysis was performed using a Student's paired $t$-test. Analysis of variance (ANOVA) of a crossover design was also carried out in order to determine sources of variation of statistical difference.

**RESULTS AND DISCUSSION**

We previously reported the in vitro release characteristics of an ozagrel tablet suppository. Ozagrel from the suppository was released completely after 2 h. Its mean dissolution time ($MDT$) was determined to be 34.8 ± 4.0 min. Moreover, the decrease in thromboxane (TX) B2 levels in serum was obvious after rectal administration of the suppository to rabbits, and its effect was maintained at more than 90% for 8 h (unpublished observation). The above results prompted us to conduct the present research to investigate the rectal absorption of ozagrel tablet in human subjects.

The plasma concentration profiles of ozagrel after oral and rectal administration are shown in Fig. 2. As indicated by the pharmacokinetic parameters (Table 1), ozagrel absorbed more rapidly at a $T_{\text{max}}$ of 0.75 ± 0.29 h after rectal dosing than after oral dosing. The extent of absorption of ozagrel after both administered routes was similar. The $F_{\text{rel}}$ was determined to be as high as 92%. These lines of evidence suggest that the rectum is a useful administration route for maintaining adequate plasma concentrations of ozagrel for patients who cannot take tablets orally due to vomiting, unconsciousness, gastrointestinal disorders, and so on. Moreover, an ozagrel suppository is also a convenient dosage form for outpatients who have cerebral thrombosis.

It has been indicated that one of the major requirements for thromboxane synthetase inhibitors is a prolonged inhibition of thromboxane formation, which is often lacking for candidate compounds under clinical trial due to their rapid elimination. In this study, after rectal dosing, ozagrel was eliminated significantly more slowly than with oral dosing ($t_{1/2}$ 1.7 vs. 0.8 h). Therefore, in the case of ozagrel, a longer pharmacological effect could be expected after rectal administration.

Our previous experiment using rabbits has shown that the absolute bioavailability of an ozagrel suppository is much higher than that of an oral tablet. The difference in bioavailability between rabbits and humans could be explained by there being less rectal fluid and uncontrollable position of the suppository in the rectum in humans compared with animals. On the other hand, our human data showed that the standard deviation (S.D.) of $AUC_{\text{oral}}$ was larger than that of $AUC_{\text{rel}}$. This is possibly due to an inter-individual difference in the volume of rectal fluid, which is a key factor for rectal drug absorption.

The authors have reported suppository formulations which contain a tablet in a base for several other drugs including morphine, omeprazole, and ondansetron. This kind of suppository can be easily and rapidly prepared with its drug content being accurate and reproducible. Therefore, it is a practical preparation for clinical use. We have also reported the clinical use of in-house suppositories containing ketoprofen and eptazocin. On the other hand, we have studied the pharmacokinetics and pharmacodynamics (PK/PD) of ozagrel after i.v. and oral administration in rabbits and in healthy human subjects, and developed a PK/PD model to predict plasma concentrations of the drug, as well as TXB2 levels as a surrogate marker of its pharmacological effect. It is thus possible to predict the optimal dosing schedule of thromboxane synthetase inhibitors even after rectal administration.

In conclusion, the present study suggests that the rectal administration of an ozagrel suppository is a promising alternative to oral administration in humans. This study demonstrated for the first time the possibility of using an ozagrel suppository in human subjects. Further study

![Fig. 2. Plasma Concentration Profiles of Ozagrel after Rectal (○) and Oral (□) Administration (100 mg) in Healthy Human Subjects](image)
should be undertaken to confirm the pharmacological effect and clinical usefulness of rectally administered ozagrel.

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REFERENCES