*International Journal of Pharmaceutics*, 42 (1988) 251–256
Elsevier



IJP 01435

# Clinical investigation of sodium diclofenac sustained-release suppositories

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(Received 18 June 1987)
(Modified version received 22 September 1987)
(Accepted 24 September 1987)

*Key words*: Sustained release; Suppository; Sodium diclofenac; Patient; Rheumatoid arthritis

## Summary

Sustained release suppositories of sodium diclofenac (SR-Supp) were evaluated in 8 patients who were in pain. In terms of the study of plasma diclofenac concentration profiles in 4 healthy male humans, plasma diclofenac concentrations of more than 50 ng/ml were maintained for 8 h in one subject, for 9 h in another, and for more than 12 h in two others after administration of a Sr-Supp containing 50 mg sodium diclofenac. In the clinical investigations of SR-Supp, 8 patients having chronic rheumatoid arthritis with severe pain were treated with SR-Supp. Plasma diclofenac concentrations in patients were determined only at 4 h after administration of SR-Supp, but in all cases, they correlated well with the values obtained in healthy subjects. The effect of SR-Supp in alleviating pain was sustained for 10 h or more, and allowed the patients to sleep comfortably through the night.

## Introduction

The purpose of developing a sustained-release suppository is to achieve sustained-action medication. Clinically, alleviation of pain during sleep is often helpful in reducing anxiety. Administration of sustained-release suppository containing sodium diclofenac (SR-Supp), which we developed by the addition of lecithin to the suppository base (Nishihata et al., 1985; 1986), sustained plasma diclofenac concentrations in healthy dogs and in healthy human volunteers (Nishihata et al., 1985 and 1986). Administration of SR-Supp also avoided the transient, high peak levels in plasma, possibly reducing the risk of side effects.

In the present study, we examined the effect of SR-Supp on patients with pain. The primary purpose for the administration of SR-Supp was to allow the patients to sleep comfortably through the night by alleviating pain.

## Materials and Methods

### *Materials*

Sodium diclofenac was supplied by Ciba-Geigy (Japan) Ltd. (Takarazuka, Japan). Hydrogenated soya lecithin (lecithin) was supplied by Nikko

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TABLE 1

*Patients*

| Patients (sex) | Age | Weight (kg) | Diagnosis | Symptom |
|---|---|---|---|---|
| A (f) | 71 | 43 | osteoarthritis | pain |
| B (m) | 80 | 44 | chronic rheumatoid arthritis and lung cancer | pain |
| C (f) | 81 | 43 | bone fracture | pain and fever |
| D (m) | 46 | 45 | herpes zoster | pain |
| E (m) | 60 | 57 | chronic rheumatoid arthritis | pain |
| F (f) | 57 | 47 | chronic rheumatoid arthritis | pain |
| G (m) | 32 | 60 | odontalogia | pain |
| H (m) | 34 | 65 | ureter stone, acute prostatitis | pain |

Chemicals Co., Ltd. (Tokyo, Japan). Witepsol H-15 with melting point of 33–35 °C, was used as triglyceride base. Other reagents used were of analytical grade.

*Patients*

Patients displaying pain as symptoms are listed in Table 1 along with their respective diagnoses.

*Preparation of sodium diclofenac sustained-release suppository (SR-Supp)*

The SR-Supp was prepared according to the method described previously (Nishihata et al., 1986). In brief, 350 mg lecithin was dissolved in 650 mg of triglyceride base (Witepsol H-15) at 80 °C. Fifty mg sodium diclofenac was dissolved in 950 mg of the above mixture at 80 °C and then the molten mass was poured into disposable plastic molds (Nichii Packing Co., Ltd., Osaka, Japan; 1.2 ml volume). After solidification at room temperature, SR-Supps were kept at 4 °C before use.

*Clinical investigations*

A SR-Supp was given to patients predominantly once a day at 9 p.m., during medication. After administration of SR-Supp to 4 healthy male human subjects, blood samples were collected at designated time intervals for 12 h. However, collection of blood from 8 patients was performed only at 4 h after the first administration of SR-Supp, to avoid patient stress caused by frequent collection of blood. But in 3 patients, blood was also collected at 4 h after administration of SR-Supp after 7 or 40 days, to estimate the accumulation of diclofenac in blood by sequential administration. After centrifugation of samples, plasma was separated for determination of diclofenac concentration. After administration of SR-Supp, physicians or nurses asked the patients about subjective pain relief to judge the effect of SR-Supp. The changes of body temperature in one patient (patient C in Table 1) was monitored by nurses. In all subjects including healthy humans and patients, the retention times of the suppositories after the administration were more than 9 h.

*Assay*

Diclofenac in plasma was assayed by a high performance liquid chromatography (HPLC) method described previously (Yaginuma et al., 1981) with minor modification. A preparation of sample for HPLC assay was modified. Half ml plasma was mixed with 2 ml acetonitrile. After centrifugation, 2.2 ml supernatant was collected, followed by dryness. The residue was dissolved in 500 $\mu$l of mobile phase (mixture of acetonitrile and 0.05 M citrate buffer, pH 5.5; 25 : 75) for HPLC assay. The detection limit of diclofenac in plasma was 40 ng/ml, in the present study.

## Results and Discussion

It has recently been reported that the minimum effective concentration of diclofenac in humans was between 14.0 and 158.2 ng/ml in plasma to alleviate post-operative pain (Toris and Honma, 1987), which are the only published data we have. In our previous reports (Nishihata et al., 1985 and 1986), 50 ng/ml in plasma for the minimum effec-

tive concentration of diclofenac was used to estimate the duration of action of SR-Supp. Since the value of 50 ng/ml was involved in the published range, we also used this value to evaluate the duration of action of SR-Supp prepared in the present healthy human study.

The hydrogenated soya lecithin was used as additive in the present study, because SR-Supp containing hydrogenated soya lecithin has a slightly yellow color in spite of the dark color of SR-Supp containing natural soya lecithin; i.e., to avoid patient uncompliance according to the opinion of physicians.

Since plasma diclofenac concentrations in healthy human subjects were monitored only for 6 h after the administration of SR-Supp containing hydrogenated soya lecithin in the previous study (Nishihata et al., 1986), the healthy human study was repeated in the present study. Plasma diclofenac concentrations in 4 healthy male human subjects were sustained for about 8 h in one subject, for about 9 h in another and for more than 12 h for two others after the administration of SR-Supp at more than 50 ng/ml (Fig. 1). $C_{max}$, $T_{max}$ and AUC in Table 2 were obtained from profiles of plasma diclofenac concentrations in Fig. 1. Since the logarithm value of diclofenac concentrations as a function of time after 4 h showed a good straight line (Fig. 1), half life time ($t_{1/2}$) of diclofenac elimination in plasma was estimated from the straight line (solid line in Fig. 1). The mean value of $t_{1/2}$ in healthy subjects was 5.7 h (Table 2). The variation of the value of $t_{1/2}$

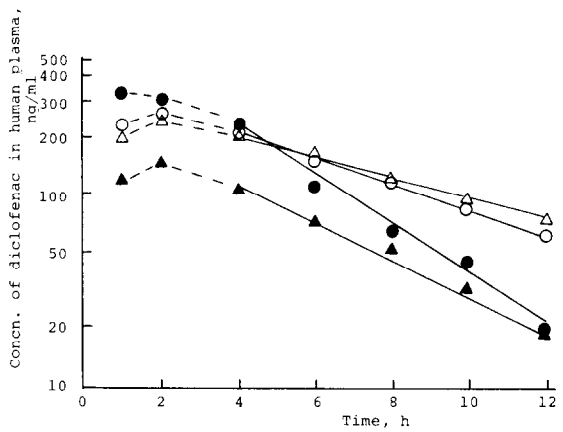


Fig. 1. Plasma diclofenac concentration in healthy male human subjects after administration of SR-Supp (at a dose of 50 mg sodium diclofenac). Subjects examined were described in Table 2 and symbols of subjects were: ○, M; ●, N; △, O; and ▲, P; * represent that 1.5 ml of plasma was used for assay. The straight solid lines were, per subject: M, log(concn) = $-0.104 \times t + 2.58$, $r = 0.986$; N, log(concn) = $-0.189 \times t + 2.85$, $r = 0.997$; O, log(concn) = $-0.086 \times t + 2.57$, $r = 0.991$; P, log(concn) = $-0.162 \times t + 2.46$, $r = 0.980$.

in the subjects may be due to the variation of metabolism in the subjects, because it has been reported that elimination of diclofenac from plasma occurred predominantly by metabolism (Riess, 1978) and that recovery of diclofenac in human urine collected for 24 h after administration of a commercial suppository of sodium diclofenac was less than 1% (Nishihata et al., 1986).

Plasma diclofenac concentrations in 8 patients at 4 h after first administration of SR-Supp are

TABLE 2

*Parameters of diclofenac in plasma of healthy male subjects (Fig. 1) after administration of SR-Supp at a dose of 50 mg sodium diclofenac*

| Subject | Age | Weight (kg) | $C_{max}$ (ng/ml) | $T_{max}$ (h) | AUC ($\mu g \cdot h/ml$) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|---|
| M | 24 | 58 | 264 | 2 | 1.92 | 6.6 |
| N | 32 | 64 | 322 | 1 | 2.04 | 3.7 |
| O | 28 | 68 | 241 | 2 | 1.87 | 8.0 |
| P | 33 | 61 | 151 | 2 | 1.09 | 4.2 |
| Mean ± S.D. | | | 244 ± 71 | 1.75 ± 0.5 | 1.73 ± 0.43 | 5.7 ± 1.8 |

$C_{max}$, peak plasma diclofenac concentration; $T_{max}$, time when $C_{max}$ was obtained; AUC, area under the curve of plasma concentration for 12 h after administration; $t_{1/2}$, half life time of diclofenac elimination in plasma, which was calculated from the solid straight lines after 4 h in Fig. 1.

TABLE 3

*Possible judgement of effect of SR-Supp in patients*

| Subject | Concn. of DC * (ng/ml) | $E_{time}$ (h) | Sleep condition | Period of medication (days) |
|---|---|---|---|---|
| A | 242 (259) | 10 | good | 55 |
| B | 233 (219) | 12 | good | 56 |
| C | 176 | 10 | good | 5 |
| D | 204 | 10 | good | 12 |
| E | 307 (272) | 12 | good | 10 |
| F | 208 | 12 | good | 3 |
| G | 412 | – | – | 1 |
| H | 132 | – | – | 1 |

$E_{time}$, the period of complete pain-relief after the first administration of SR-Supp.

* Concentration of diclofenac in plasma at 4 h after the first administration of SR-Supp, but the values in parentheses represent the concentration at 4 h after 7 days of administration for patient E and after 40 days for patients A and B.

shown in Table 3. Since the purpose of the administration of SR-Supp to patients was an investigation of effective duration of SR-Supp rather than an investigation of pharmacokinetics and pharmacodynamics, a frequent collection of blood was avoided. Thus, the effect was judged predominantly for pain relief.

The effect of SR-Supp on alleviation of pain was examined in patients with various diagnoses (Table 1). Alleviation of pain was judged subjectively by the patients themselves. Sleeping condition was also asked, because the primary purpose for the administration of SR-Supp was to allow the patients to sleep comfortably through the night. Administration of SR-Supp was performed once a day and predominantly at 9 p.m.

Patients A and B were treated with commercial suppository of sodium diclofenac (Voltaren) for several days, but they were wakened during the nigh by pain even after taking a Voltaren suppository at 9 p.m. Thus, SR-Supp was used for their medication as pain reliever.

Patient A, with osteoarthritis, was treated with SR-Supp once a day for 55 days to alleviate pain. During the first 9 days, SR-Supp was also administered at 09.00 h but thereafter, SR-Supp was administered only at 21.00 h to facilitate comfortable sleep. The administration of SR-Supp alleviated pain completely for about 10 h (Table 3).

The first administration of SR-Supp to patient B also induced a comfortable sleep, and effective periods of pain relief became longer with sequential administration of SR-Supp for 56 days. In this patient, even though lung cancer was not medicated by diclofenac, complete alleviation of pain and comfortable sleep during night time were achieved by the sequential administration of SR-Supp, indicating that SR-Supp was a totally satisfactory therapy for pain in this patient (Table 3).

In patient C with a bone fracture of the right leg, complete alleviation of pain was sustained for about 10 h after the first administration of SR-Supp, followed by minor pain for several hours, uninterrupted sleep after administration of SR-Supp at 21.00 h. In this patient, the effect of SR-Supp in reducing fever as well as alleviating pain was investigated. As shown in Fig. 2, the administration of SR-Supp reduced the body temperature for more than 12 h after the first administration of SR-Supp. The effect of SR-Supp in reducing fever seemed to be longer than that in relieving pain in this patient. After the fifth administration of SR-Supp, patient C did not require additional medication, because his pain and fever were only slight.

Patient D, with herpes zoster, was treated with SR-Supp as pain reliever once a day for 12 days,

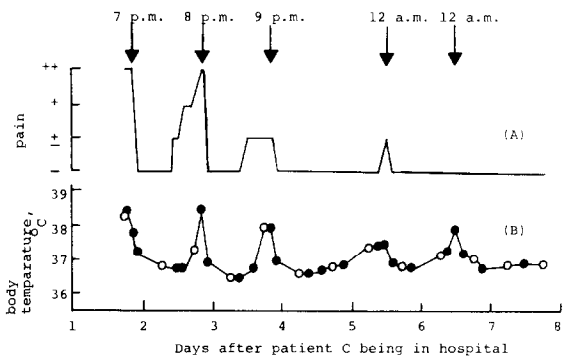


Fig. 2. The pain relief (A) and the reduction of fever (B) in patient C during the medication with SR-Supp. Arrows represent the times of administration of SR-Supp. In (A), evaluation of pain was performed in 4 classes: –, no pain or only slightly; ±, endurable pain; +, pain often unendurable; + +, severe pain. In (B), open circles indicate the times at 06.00 and 18.00 h.

and displayed a tendency similar to that of patient C. The initial pain-free period was about 10 h, but the period became longer with sequential administration.

Patient E, with chronic rheumatoid arthriris, was treated with SR-Supp immediately after being admitted to the hospital. At the beginning of treatment with SR-Supp, alleviation of pain was sustained for more than 12 h (Table 3), with uninterrupted sleep after administration at 21.00 h. The pain-free period in this patient became longer with sequential administration once a day, and SR-Supp was terminated after 10 days because the patient was judged to be pain-free.

The plasma diclofenac concentrations in patients A, B and E were also measured at 4 h after administration at 40 days (for A and B) and 7 days (for E), and the concentrations were very close to the concentrations at 4 h after the first administration. This results may indicate that diclofenac in the body after administration of SR-Supp disappears within 24 h.

In patient F, the period of pain relief was about 12 h, inducing comfortable sleep after administration of SR-Supp at 21.00 h once a day for 3 days (Table 3).

Patients G and H (Tables 1 and 3) experienced total pain relief after only one administration of SR-Supp, probably by inhibition of inflammation in patient G, and probably because of the disappearance of a urether stone from patient H. For patient H, we do not imply that administration of SR-Supp caused the urether stone to disappear.

It has been reported that apparent bioavailability after rectal administration of promethazine to humans was influenced by the administration forms; i.e., the rectal formulation in retaining the drug in the rectal area caused a low apparent bioavailability as estimated by plasma drug concentration profiles (Moolenaar et al., 1981). Since de Boer et al. (1979) have reported that only partial avoidance of first-pass metabolism in liver was achieved after rectal administration of high-clearance drug in humans, the apparent decrease of bioavailability after rectal administration of high-clearance drug in the retention form might be due to differences of first-pass effect in liver as suggested by Moolenaar et al. (1981). Since elimination of diclofenac in humans occurred predominantly by metabolism (Riess, 1978), SR-Supp in retaining diclofenac in the rectal area may result in the decrease of apparent bioavailability. However, the purpose of administering SR-Supp are to avoid a transient high diclofenac concentration and to retain the diclofenac concentrations in plasma, rather than an increase of apparent bioavailability of diclofenac.

In the present investigations, the administration of SR-Supp produced pain relief in all patients enrolled in the present study. The effective pain-relief period was about 10–12 h after the first administration of SR-Supp. The action of SR-Supp was sufficiently long to provide patients with comfortable sleep at night, indicating that SR-Supp is an effective formulation to achieve sustained-action medication. In patient C (Fig. 2) the effective duration of SR-Supp to reduce fever was more than 12 h after the first administration, which was longer than the effective duration to alleviate pain. Although we had only one patient to investigate the effect of SR-Supp as both antipyretic and analgesic, minimum effective concentration of diclofenac to reduce fever may be less than that to relieve pain. Further, none of the patients and healthy volunteers complained about side effects, such as diarrhea, discomfort, headache, stomach pain, and irritation of the rectum which are sometimes observed after administration of the conventional suppository of sodium diclofenac or indomethacin. This result may indicate that the potential for side effects is reduced by avoiding transient high concentrations of diclofenac in plasma.

## References

De Boer, A.G., Breimer, D.D., Mattie, H., Pronk, J. and Gubbens-Stibbe, J.M., Rectal bioavailability of lidocain in man: partial avoidance of first-pass metabolism. *Clin. Pharmacol. Ther.*, 26 (1979) 701–709.

Moolenaar, F., Ensing, J.G., Balhuis, B.G. and Visser, J., Absorption rate and bioavailability of promethazine from rectal and oral dosage form. *Int. J. Pharm.*, 9 (1981) 353–357.

Nishihata, T., Wada, H., and Kamada, A., Sustained-release of sodium diclofenac from suppository. *Int. J. Pharm.*, 27 (1985) 245–253.

Nishihata, T., Sudho, M., Kamada, A., Keigami, M., Fujimoto, T., Kamide, S. and Tatsumi, N., Investigation of sustained-release suppository of sodium diclofenac in human. *Int. J. Pharm.*, 33 (1986) 181–186.

Riess, W., Pharmacokinetics and metabolism of the anti-inflammatory agent Voltaren. *Scand. J. Pharmacol.*, 22 (1978) 17.

Toris, T. and Honma, T., Time course of post-operative pain and plasma levels after single administration of Voltaren Supp. *Jpn. J. Inflammation*, 7 (1987) 289–292.

Yaginuma, H., Hohno, Y., Itoh, S., Kubo, K., Yamazaki, M., Kamada, A., Shimazu, H., and Matsuo, T., Rectal delivery of antiinflammatory drugs. Effect of amino acid on the change in the rectal mucosa induced by diclofenac sodium. *Chem. Pharm. Bull.*, 30 (1982) 3302–3309.