Flurbiprofen concentration in soft tissues is higher after topical application than after oral administration

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Efficacy of the oral administration of flurbiprofen has been established. However, the efficacy of topical application of flurbiprofen has not been sufficiently established because of a lack of scientific data.
- No studies have measured NSAID concentrations in the human tendon, periosteum and bone tissues, which frequently have inflammatory conditions due to overuse and trauma, after oral administration and topical application.

WHAT THIS STUDY ADDS

- The flurbiprofen concentration in the fat, tendon, muscle and periosteum tissues after topical application was significantly higher than that after oral administration under the regulatory approved dosing guidelines, while the concentration in the bone tissue and the plasma was significantly lower after topical application.
- Topical application effectively increases the flurbiprofen concentration in the tendon, muscle, and periosteal tissues.

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Keywords

flurbiprofen, plasma concentration, tissue concentration, topical application

Received

13 January 2012

Accepted

5 July 2012

Accepted Article Published Online

24 July 2012

AIM

To compare tissue concentrations of flurbiprofen resulting from topical application and oral administration according to the regulatory approved dosing guidelines.

METHOD

Sixteen patients were included in this study. Each patient was randomly assigned to the topical application or oral administration group. In each group, a pair of tapes or a tablet, containing a total of 40 mg flurbiprofen, was administered twice at 16 and 2 h before the surgery.

RESULTS

The flurbiprofen concentration in the fat, tendon, muscle and periosteum tissues was significantly higher ($P < 0.0330$) after topical application (992 ng g⁻¹ [95% CI 482, 1503], 944 [95% CI 481, 1407], 492 [95% CI 248, 735], and 455 [95% CI 153, 756], respectively) than after oral administration (150 ng g⁻¹ [95% CI 84, 217], 186 [95% CI 118, 254], 82 [95% CI 49, 116], and 221 [95% CI, 135, 307], respectively).

CONCLUSION

Topical application is an effective method to deliver flurbiprofen to the human body, particularly to soft tissues near the body surface.

Introduction

Efficacy of oral administration of non-steroidal anti-inflammatory drugs (NSAIDs) has been fully established [1]. Recently, topical application of NSAIDs has attracted attention because it is expected to reduce the adverse reactions in the gastrointestinal tract due to oral administration [2]. However, the efficacy has not sufficiently been established because of a lack of scientific data. Concentrations of NSAIDs in a targeted tissue are one of the most fundamental data in evaluating the efficacy of NSAIDs. To evaluate the efficacy of a topical application, it is an important strategy to compare a tissue concentration of a certain NSAID between the topical application and the oral administration. However, only a few studies have been conducted to evaluate such efficacy to date. Tegeder *et al.* [3] compared the concentration of ibuprofen in the muscle and fat tissues between topical application and oral administration. Recently, we performed a randomized pharmacokinetic study to compare the concentrations of diclofenac in muscle, synovium and fat tissues between topical application and oral administration according to the regulatory approved dosing guidelines [4].

Concerning flurbiprofen, the effectiveness of oral administration has been sufficiently established [5, 6]. However, no controlled studies have been conducted to compare the tissue concentration of flurbiprofen between topical application and oral administration, although the comparative pharmacokinetic data from a limited number of patients were available in the literature [7]. In addition, no studies have determined NSAID concentrations in the human tendon, periosteum and bone tissues, in which there are frequent inflammatory conditions due to overuse and trauma, after both oral application and topical administration.

Thus, we have conducted a randomized pharmacokinetic study in human patients to compare the flurbiprofen concentration in the fat, tendon, muscle, periosteum and bone tissues as well as the plasma between topical application and oral administration according to the regulatory dosing guidelines approved in Japan [8, 9]. In this study, we have hypothesized that the flurbiprofen concentration may be significantly higher after the topical application in the fat, tendon, muscle and periosteal tissues than after the oral administration. The aim of this study is to test this hypothesis.

Methods

This randomized pharmacokinetic study was conducted with prior approval from the Investigational Review Board, the Ethics Committee of Hokkaido University School of Medicine. The subjects were 16 patients who were scheduled to undergo anterior cruciate ligament (ACL) reconstruction with the semitendinosus tendon for chronic ACL

insufficiency. Exclusion criteria used in this study included (1) patients who had received any flurbiprofen or ketoprofen preparation within 2 weeks before the start of the study, (2) patients who had received an injection of a steroid, sodium hyaluronate, etc. into the affected joint within 1 week before the start of the study, (3) patients with wounds or diseases in the skin around the knee, (4) patients with a history of hypersensitivity to a certain drug, (5) patients suffering from a peptic ulcer, (6) patients with severe underlying internal diseases (heart disease, renal disease, coronary artery disease, hematological disease, etc.) or history of such diseases, (7) patients with a history of hypersensitivity to a certain NSAID, (8) patients with a history of asthma due to hypersensitivity to aspirin, (9) pregnant or possibly pregnant women or nursing women and (10) other patients judged, for any reason, to be unsuitable for the study by the attending physician. Sixteen patients were included in the study. Informed consent was obtained from each patient with a signed document. At the time of admission, each patient was randomly assigned to group T (topical application group) or group O (oral administration group), by using the following method. Namely, we prepared two ping-pong balls in a box hidden from view. We had marked 'O' on one ball and 'T' on the other ball. At the time of admission, a patient was asked to blindly take out one ball from the box. According to the mark ('O' or 'T') shown on the ball, the patient was assigned to group O or group T. Then, the ball was returned back to the box for the next patient. The two balls in the box were used repeatedly for every patient in the same manner. Thus, each patient was independently assigned to group O or T with a probability of 50%. Subsequently, nine patients belonged to group T, and seven patients belonged to group O.

We used flurbiprofen tapes (Zepolas® Tape, Mikasa Seiyaku, Tokyo, Japan) and flurbiprofen tablets (Froben® Tablet 40, Kaken Seiyaku, Tokyo, Japan), which were commercially available in Japan. The tape (7 × 10 cm) contained 20 mg flurbiprofen. This flurbiprofen tape is classified as an immediate release transdermal delivery system. The tape releases flurbiprofen over an extended period of time. After topical application, the $C_{\max}$ in the plasma was 870 ng ml⁻¹ and $t_{\max}$ was 11.6 h after applying the same two tapes as used in the present study [8, 9]. The tablet contained 40 mg flurbiprofen. Concerning the oral prescription of the tablets, it was recommended in Japan that one tablet should be taken twice (every 12 h) a day (a total of 80 mg). Regarding the topical prescription, it was recommended to patch one or two tapes on a lesion, changing them once or twice a day. Therefore, based on the regulatory approved dosing guidelines, the administration protocols were decided as follows: concerning group O, a tablet was orally administered in the fed state at 14 h before sampling, and then, another one tablet was orally administered in the fasting state at 2 h before sampling. Regarding group T, two tapes were patched on the medial

and lateral aspects of the knee, respectively, at 14 h before sampling. Then, at 2 h before sampling, the two tapes were removed, and new two tapes were patched in the same manner. This protocol was decided on for the following reasons: first, we intended to compare the state at 14 h after starting treatment with flurbiprofen according to the common clinical recommendation between oral administration and topical application and secondly, we intended to harvest the samples when the plasma concentration was closed to the $C_{\max}$ in each group, because the $t_{\max}$ of flurbiprofen is 1.4 h after oral administration and 11.6 h after topical application [9]. In this protocol, the apparent dose of flurbiprofen in each administration contained 40 mg flurbiprofen. However, it should be noted that the amount of absorbed flurbiprofen was different between the topical application and oral administration.

At the beginning of ACL reconstruction surgery, a blood sample (5 ml) was collected with a heparinized vacuum syringe from each patient. Then, the following tissues of 1–2 g were biopsied as samples through the surgical incision for ACL reconstruction; subcutaneous fat tissue beside the skin incision, an edge of the sartorius muscle, tendon and periosteal tissues around the semitendinosus tendon attachment, and a drilled bone tissue obtained from a bone tunnel for ACL reconstruction. Harvesting of the samples did not provide any additional invasion to the patients. All the samples were stored at -40°C until the time of measurement.

To measure flurbiprofen concentration, the tissue samples were weighed, homogenized with methanol and sonicated for 5 min. The supernatants were diluted with methanol to 20 ml. Ketoprofen (0.1 ml), as the internal standard (IS), was added to the aliquots (4 ml) of the supernatants and the samples were dried. The dry residues were submitted to liquid–liquid extraction with 0.1N HCl (1 ml) and 6 ml n-hexane:ethyl acetate (7:3, v/v). The organic phase (5 ml) was dried and the residue was dissolved in methanol (0.2 ml). Regarding the plasma samples, the aliquots (0.2 ml) were mixed with the IS, followed by the above-described liquid–liquid extraction. Then, the flurbiprofen concentration was measured with liquid chromatography (Alliance 2695 Separations Module, Waters Corporation, Milford, USA) and mass spectrometry (TSQ Quantum, Thermo Fisher Scientific Inc., Waltham, USA). Chromatographic separations were obtained under isocratic conditions using an Inertsil ODS-3 column (GL Sciences Inc, Torrance, USA) at a flow of 0.2 ml min^{-1} . The temperature was set at 40°C . The mobile phase consisted of methanol and 5 mM ammonium acetate (80:20; v/v). Mass spectrometry was operated in the negative ESI mode using the selective reaction monitoring mode (SRM) of $243 \rightarrow 199$ (collision energy 28 eV) and $m/z 253 \rightarrow 209$ (24 eV) for flurbiprofen and for the IS, respectively. Spiked plasma samples were used to perform calibration curves and to create quality control samples, and they were processed by the same procedure. Concerning the tissue samples, the

inter-assay ($n = 5$) showed the precision of a range between 1.22 and 3.05% as well as the accuracy of a range between -8.20 and 0.00% , while the intra-assay (3 days, $n = 3$ each) revealed the precision of a range between 3.43 and 6.16% as well as accuracy of a range between -6.60 and -2.31% . Regarding the plasma samples, the inter-assay ($n = 5$) showed the precision of a range between 1.92 and 2.67% as well as the accuracy of a range between -9.22 and 9.54% , while the intra-assay (3 days, $n = 3$ each) revealed the precision of a range between 2.38 and 3.66% as well as the accuracy of a range between -7.04 and 9.48% . The quantification limit value was 2 ng g^{-1} for the tissues and 50 ng ml^{-1} for the plasma samples.

The statistical comparisons between groups were made using the Mann–Whitney U -test and the Chi-square test. The significance level was set at $P = 0.05$.

Results

All of the 16 patients who enrolled in the study showed no clinical problems due to the topical application and oral administration without any abnormal data shown in the laboratory evaluation during the study period. All data are shown in Table 1. In group T, we had no patients having the issue of contamination during and after surgery.

The flurbiprofen concentration in each tissue was compared between the patients receiving topically applied flurbiprofen (group T) and the patients receiving orally administered flurbiprofen (group O) (Table 1). The flurbiprofen concentrations in the subcutaneous fat, tendon, muscle and periosteal tissues were significantly higher ($P = 0.0009$, 0.0018 , 0.0026 and 0.0012 , respectively) in the patients receiving topically applied flurbiprofen (mean 992 ng g^{-1} [95% CI 482, 1503], 944 [95% CI 481, 1407], 492 [95% CI 248, 735] and 455 [95% CI 153, 756], respectively) than in the patients receiving orally administered flurbiprofen (150 ng g^{-1} [95% CI 84, 217], 186 [95% CI 118, 254], 82 [95% CI 49, 116] and 221 [95% CI 135, 307], respectively). On the other hand, the flurbiprofen concentrations in the plasma and the bone tissue were significantly lower ($P = 0.0018$, and 0.0012 , respectively) in the patients receiving topically applied flurbiprofen (mean 1369 ng ml^{-1} [95% CI -126 , 2863] and 64 ng g^{-1} [95% CI 25, 103], respectively) than in the patients receiving orally administered flurbiprofen (3331 ng ml^{-1} [95% CI 1730, 4932] and 120 ng g^{-1} [95% CI 84, 217], respectively).

To show the remarkable differences between the topical application and the oral administration, we calculated the tissue:plasma concentration ratio (T:P ratio), which was defined as a ratio of the tissue concentration divided by the plasma concentration. The T:P ratio in the patients receiving orally administered flurbiprofen averaged 6% (95% CI 1, 10) for the fat, 7% (95% CI 3, 12) for the tendon, 3% (95% CI 1, 4) for the muscle, 9% (95% CI 3, 16) for the periosteum and 4% (95% CI 1, 8) for the bone. On

Table 1
Patient demographics and flurbiprofen concentrations in each tissue

Group	Age (years)	Gender	Height (cm)	Weight (kg)	BMI (kg m ⁻²)	Fat (ng g ⁻¹)	Tendon (ng g ⁻¹)	Muscle (ng g ⁻¹)	Periosteum (ng g ⁻¹)	Bone (ng g ⁻¹)	Plasma (ng ml ⁻¹)
Oral (n = 7)	Average (SD)	6 M, 1F	166 (10)	64 (7)	23 (3)	150 (72)	186 (74)	82 (36)	221 (93)	120 (88)	3331 (1731)
	95% CI		156, 175	58, 70	21, 26	84, 217	118, 254	49, 116	135, 307	39, 201	1730, 4932
Topical (n = 9)	Average (SD)	7 M, 2F	168 (8)	64 (8)	23 (3)	992 (664)	944 (602)	492 (317)	455 (392)	64 (51)	1369 (1944)
	95% CI		162, 174	58, 71	21, 25	482, 1503	481, 1407	248, 735	153, 756	25, 103	-126, 2863
Comparison	NS	NS	NS	NS	NS	P = 0.0009	P = 0.0018	P = 0.0026	P = 0.0012	P = 0.0018	P = 0.0012

Each value shows the average (SD) with the 95% CI. Each P value shows a significant difference between the oral administration group and the topical application group. BMI, body mass index; CI, confidence interval; NS, not significant.

the other hand, the T : P ratio in the patients receiving topically applied flurbiprofen averaged 173% (95% CI 20, 326) for the fat, 160% (95% CI 35, 285) for the tendon, 77% (95% CI 27, 126) for the muscle, 65 % (95% CI 24, 105) for the periosteum and 11 % (95% CI -2, 24) for the bone. There were significant differences between the topical and oral applications concerning the fat, tendon, muscle and periosteal tissues (*P* < 0.0100), while we found no significant difference concerning the bone tissue.

Discussion

The present study demonstrated that, under the regulatory approved dosing guidelines, flurbiprofen concentrations in the tendon, muscle and periosteal tissues as well as the fat tissue were significantly higher in the patients receiving topically applied flurbiprofen than in the patients receiving orally administered flurbiprofen. On the other hand, the concentration in the plasma and the bone tissue was significantly higher in the patients receiving orally administered flurbiprofen than in the patients receiving topically applied flurbiprofen. We found a relatively large degree of interindividual variability in the topical application. Possible causes of the relatively large degree of interindividual variability in the topical application may include the thickness of the subcutaneous fatty tissue, interindividual variability of skin functions, and so on. However, we can conclude that topical application is a method to increase effectively the flurbiprofen concentration in the tendon, muscle and periosteal tissues, which are located near the body surface.

We validated the reliability of the flurbiprofen concentrations measured in the present study by comparing them with the results in the literature. As there have been few studies regarding the distribution of flurbiprofen into the tendon, muscle, periosteum and bone tissues after oral administration [10], we compared the measured plasma concentration of flurbiprofen with that reported in the existing literature. After oral administration of a tablet containing 40 mg flurbiprofen, the *C*_{max} in the plasma was 5600 ng ml⁻¹ and the *t*_{max} was 1.4 h [9]. After oral administration of a tablet containing 50 mg flurbiprofen, several studies reported that the *C*_{max} ranged from 4200 to 8200 ng ml⁻¹ and that the *t*_{max} ranged from 1.3 to 2.8 h [11–14]. In the present study, the mean plasma concentration was 3331 ng ml⁻¹ in the patients receiving orally administered flurbiprofen. This result is comparable with the previous data [9, 11–14]. Concerning topical application with the same two tapes as used in the present study, it was reported that the *C*_{max} in the plasma was 870 ng ml⁻¹ at the *t*_{max} of 11.6 h [8]. These data are also comparable with the present result (1369 ng ml⁻¹) on the plasma concentration in the patients receiving topically applied flurbiprofen. The similarity of the plasma concentration between the results in the present study and those

in the previous literature suggests that the tissue concentrations measured in the present study are reliable, because all the flurbiprofen concentrations were simultaneously determined with the same measurement system in the present study.

We considered why the flurbiprofen concentrations in the tendon, muscle and periosteal tissues were significantly higher in the patients receiving topically applied flurbiprofen than in the patients receiving orally administered flurbiprofen. We calculated T : P ratio in these tissues in the patients receiving topically applied flurbiprofen. It is known that the T : P concentration ratio after oral administration shows a delivery rate of a certain drug from the blood to a certain tissue. The T : P concentration ratio in the tendon, muscle and periosteal tissues was dramatically greater after topical application than after oral administration. This fact indicated that, after topical application, flurbiprofen was delivered to these tissues not only via blood but also via another transport system. Recent studies have reported that a transport system by dermal blood or lymphatic vessels plays a more significant role than a direct diffusion mechanism in the delivery mechanism of NSAIDs from the skin to deep tissues [15,16]. Therefore, the present study suggested that the transport system by dermal vessels may be dominant in topical delivery of flurbiprofen to the tendon, muscle and periosteal tissues. On the other hand, the T : P ratio in the bone was comparable between topical and oral administration. This result suggested that, in the delivery of flurbiprofen to the bone, the role of the transport system by dermal vessels was reduced. The causes may include that the bone tissue is surrounded by a dense calcified matrix. Thus, this study suggested that the tendon, the muscle and the periosteum are the tissues suitable for topical application therapy with appropriate NSAIDs.

There were some limitations in the present study. The first limitation is that we did not determine the concentration–time curves of the plasma and the tissues or the peak values after administration. Therefore, we cannot refer to comparisons of the tissue concentration of flurbiprofen between topical application and oral administration at different periods. However, we compared the tissue concentrations at the period when the plasma concentration was nearly at the C_{max} after both topical application and oral administration. Therefore, we believe that this comparison is of clinical value. The second limitation is that we did not collect any data on pain reduction in this study, because the aim was to collect pharmacokinetic data. In addition, the minimal flurbiprofen concentration that has anti-inflammatory effects in these tissues is not known [17, 18]. Therefore, we cannot refer to clinically pain-reducing effects provided by the measured tissue concentration. However, it is not easy to conduct such a study to evaluate simultaneously the tissue concentration of a certain NSAID and its effect on pain reduction in patients. The third limitation is that we could not measure what

percent of flurbiprofen is bound to protein in the measured tissues. It is known that, in blood, 99% of flurbiprofen is bound to protein (mainly to albumin), and only the remaining 1% is available to exert a clinical effect [5–7]. We speculate that a similar percentage of flurbiprofen may be available to exert a clinical effect in the tissues, because flurbiprofen is confirmed to have a pain-reducing effect on these tissues. Further studies are needed to establish the clinical utility of topical application of flurbiprofen in comparison with oral administration.

In conclusion, under these conditions according to the clinically recommended prescriptions, the flurbiprofen concentration was significantly higher after topical application in the tendon, muscle and periosteal tissues than after oral administration, although the plasma flurbiprofen concentration was significantly higher after oral administration than after topical application. The present study has shown evidence that topical application with a tape containing flurbiprofen is an effective method to deliver flurbiprofen to the human body, particularly to tissues near the body surface.

Competing Interests

There are no competing interests to declare.

This research was financially supported by a Grant for Clinical Research from Hokkaido University Graduate School of Medicine, Sapporo, Japan.

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