Pharmacokinetics of Indomethacin Ester Prodrugs: Gastrointestinal and Hepatic Toxicity and the Hydrolytic Capacity of Various Tissues in Rats

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Received February 22, 1996; accepted May 28, 1996

In order to develop a potential prodrug of indomethacin (IM) which causes less irritation to the gastrointestinal mucosa, the ester prodrugs [butyl ester (IM-BE) and octyl ester (IM-OE)] of IM were synthesized and evaluated for their ulcerogenic activity and hepatic injury after oral administration in rats. Additionally, the kinetics of hydrolysis of the prodrugs were examined to characterize the tissues or organs capable of hydrolyzing the ester bonds. The plasma levels of IM after the oral administration of IM-OE and IM-BE were comparatively low compared with those after IM, with a small bioavailability (2.1 and 15.0%, respectively). Ulcerogenic activity and hepatic injury, expressed by decreased hepatic microsomal enzyme activities, were hardly seen after repeated oral administration of the prodrugs, in contrast with the severely irritating effects of IM alone. Hydrolysis of the prodrugs was adequately described by first-order kinetics. IM-BE was relatively rapidly hydrolyzed in plasma, skin and whole blood, but the hydrolysis in the intestinal mucosa and liver was very slow. The hydrolytic rates for IM-OE were exceedingly small or negligible.

These results indicate that the main part of IM-BE and IM-OE administered orally might not be hydrolyzed to IM in the gastrointestinal tract, and that the ester prodrugs themselves were absorbed through the mucosa; also, that the hydrolysis of ester bonds would be carried out mainly in the circulatory system. Consequently, IM-BE seems to be an ideal prodrug of IM.

Key words pharmacokinetics; ester prodrug; gastrointestinal irritation; hepatic toxicity; hydrolysis; rat

The potentially deleterious effects of acidic nonsteroidal anti-inflammatory drugs (NSAIDs) on the stomach, especially the glandular mucosa, are well known.1–3 The gastrochemical side effects are the result of a direct contact effect and a systemic effect which may also be manifested after intravenous (i.v.) dosing.4 Of these effects, the direct contact mechanism appears to play a determinant role in the production of gastrointestinal lesions,5 and it is probably caused by a combination of local irritation produced by the free carboxylic acid group of the NSAIDs and by local inhibition of the cytoprotective action of prostaglandins on gastric mucosa.6

Prodrugs of indomethacin (IM), such as acemethacin, indomethacin farnesil and indomethacin oligoethylene ester7,8 reduce the occurrence of adverse reactions. Acemethacin, however, released IM in the liver as a result of first-pass metabolism,9 and enterohepatic circulation also occurs,10 which may cause gastrointestinal irritation.11 On the other hand, the procedure of ester formation is shown to be effective in markedly reducing the ulcerogenic activity of some potent NSAIDs.11,12 IM farnesil is a prodrug designed to reduce the occurrence of side effects by esterification of the carboxyl group of IM with farnesol.13 Even though the prodrug approach has been extensively used to obtain IM prodrugs, none of the synthesized derivatives has resulted in an ideal prodrug.

In this paper, to reduce the gastrointestinal side effects of IM and to develop prodrugs which are readily hydrolyzed following intestinal absorption to release the parent drug by lipases or esterases, we synthesized the ester prodrugs, IM octyl ester (IM-OE) and IM butyl ester (IM-BE) (Fig. 1), and the pharmacokinetics, intestinal absorption and gastrointestinal and hepatic toxicity were estimated after oral single or repeated administration in rats, in comparison with those after IM dosing. In addition, the hydrolytic kinetics of various tissues were measured to characterize the tissues capable of hydrolyzing the ester bond in vitro.

MATERIALS AND METHODS

Materials IM (J.P. grade) and IM-OE (mp 55–56 °C; Anal. Calc'd for C_{19}H_{23}NO_4; C, 69.00; H, 6.86; N, 2.98. Found: C, 69.01; H, 6.82; N, 2.98) were a gift from Sumitomo Pharmaceutical Company (Osaka, Japan). Mefenamic acid and β-estradiol dipropionate, internal standards for HPLC assay, were obtained from Sigma Chemical Company (St. Louis, MO). NADP, glucose-6-phosphate (G-6-P) and G-6-P dehydrogenase were obtained from Oriental Yeast Co., Ltd (Tokyo, Japan). Aniline was used following redistillation. All other chemicals and solvents used were of reagent grade or HPLC quality. Male Wistar rats, weighing 200–250 g,

![Fig. 1. Structure of IM-BE and IM-OE](image-url)

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were used throughout this study. The animals had free access to MF diet (Oriental Yeast Co., Ltd.) for 3—4 d prior to the experiment. On the day before the experiment, the rat jugular vein was cannulated with silicon tubing.

**Synthesis of IM-BE** IM (500 mg, 1.4 mmol) was mixed with oxalyl chloride (1.2 ml, 14 mmol) and benzene (3 ml), and the mixture was heated at 70°C under microwaves. After evaporation of the solvent, n-butanol (1 ml, 10.9 mmol) and tetrahydrofuran (5 ml) were added to the residue, followed by mixing at room temperature for 24 h. The solution was neutralized with saturated NaHCO₃ solution, followed by ether extraction and drying with MgSO₄. The products were purified on a column chromatography of silica gel (solvent: benzene). The yield was 0.46 g (77.4%). Colorless prisms, mp 74—74.5°C. Anal. Calc for C₄₃H₄₈Cl₂N₂O₂: C, 66.74; H, 5.84; N, 3.38. Found: C, 66.85, H, 5.87; N, 3.39.

**Intravenous (i.v.) Administration of IM, IM-OE and IM-BE** IM and its prodrugs (7.6 or 5 mg/kg, IM equivalent) were administered intravenously as a solution (0.2—0.25 ml) in a mixture of N,N-dimethylformamide–ethanol–water (6:2:2, v/v). A 0.2 ml blood sample was collected periodically after dosing through the cannula.

**Oral Administration of IM, IM-OE and IM-BE** IM, IM-OE and IM-BE (7.6 mg/kg, IM equivalent) were administered orally as aqueous suspensions (1.0 ml/250 g) in 1.5% carboxymethylcellulose sodium (CMC) to the rat starved for 12 h before the experiment. A 0.2 ml blood sample was collected periodically after dosing through the cannula for a total time period. The plasma was separated immediately by centrifugation and stored frozen until the time of assay. In the repeated dosing experiment, IM and the prodrugs (7.6 mg/kg, IM equivalent) were administered orally twice daily for 1 or 3 d.

**Assay of Ulcerogenic Activities** Two percent HCHO (10 ml) was poured into the stomach and intestine of rat dosed with the drug or CMC (control) using an injector, at 12 h after the final dosing. The stomach and intestines were removed and opened on the board. The lesions on the gastrointestinal mucosa were counted by visual examination using a 2 × 2 binocular magnifier, with all the ulcers >0.5 mm being recorded.

**Preparation of Microsome** Animals were fasted for 12 h prior to the experiment. The microsomal fractions of liver were prepared according to the methods of Omura and Sato.

**Protein Determination** Protein concentration was determined by the method described by Lowry et al. with bovine albumin, fraction V, as a standard.

**Hydrolysis Studies** Whole blood was collected by heart puncture and plasma was obtained by centrifugation of the blood. Intestinal contents were removed by flushing with saline, and the mucosa of a 5 cm length of duodenum was scraped off with a slide glass. The mucosa was suspended in 5.0 ml of 0.85% NaCl–10 mm phosphate buffer, pH 7.4. The liver was perfused through the portal vein with ice-cold saline to remove blood. The minced liver was homogenized in 5 volumes of 1.15% KCl, and the homogenates were centrifuged at 10000 × g for 30 min to obtain the supernatant. The rat abdominal skin (3 × 3 cm area) was homogenized in 9.0 ml of ice-cold 0.01 M phosphate buffer, pH 7.4, using a micro homogenizer (Physoctron NS-10; Nition, Funabashi, Japan). The homogenates were centrifuged at 10000 × g for 30 min and the supernatant was collected. The reaction mixture consisting of the prodrug solution (10 mg/ml ethanol, 0.1 ml), the suspension or supernatant (1.0 ml) and 0.1 M phosphate buffer, pH 7.4, (0.5 ml) was incubated at 37°C for 0.5, 1, 2 and 3 h. At appropriate time intervals, a 50 μl aliquot was withdrawn and added to 150 μl of methanol containing the internal standard, followed by centrifugation. IM in the supernatant was analyzed by the HPLC method mentioned below.

**Enzyme Assays** The concentration of cytochrome P-450 (P450) in the microsomal fraction was determined by the method of Omura and Sato. The activity of aniline hydroxylase was determined by the method of Ikeda.

**Determination of IM, IM-OE and IM-BE** IM in the plasma and sample was determined by the HPLC method of Kwong et al. with slight modifications, as reported previously. IM-OE and IM-BE were determined according to the method reported by us.

**Data Analyses** Pharmacokinetic parameters were calculated using the nonlinear least squares regression program, MULTI. The plasma concentration–time data after i.v. administration were fitted to the equations:

\[
C_t = C_0 e^{-kt} \\
C_t = A e^{-at} + B e^{-bt}
\]

where \(C_t\) and \(C_0\) are the drug concentration at time \(t\) and time zero, respectively, \(k_e\) is the elimination rate constant, and \(A, a, \) and \(B, \beta\) are the biexponential equation constants.

The area under the plasma concentration–time curve (AUC) up to the last sampling point was calculated by the trapezoidal method, and the AUC beyond the last observed plasma concentration (Cₘ) was extrapolated according to \(C/\beta\). In some experiments, the AUC was given by \(AUC = A/a + B/\beta\). The area under the first moment curve (AUMC) and the mean residence time (MRT) were calculated by means of moment analysis.

In the hydrolysis experiment, the first-order rate constant (\(k\)) was calculated by using the least squares fit program, MULTI.

The means of all data are presented with their standard deviation (mean ± S.D). Statistical analysis was performed using a non-paired Student’s t-test, and the significance level adopted was \(p < 0.05\).

RESULTS AND DISCUSSION

**Plasma Concentration after i.v. Administration** The plasma concentrations after i.v. administration of IM, IM-OE and IM-BE are shown in Fig. 2. The plasma levels of IM after IM or IM-BE dosing declined in a biexponential manner. On the other hand, the plasma decay curve of IM that was formed from IM-OE was found to be monoeponential, and the plasma levels were much lower than those after the administration of IM alone.
The much lower plasma levels of IM formed from IM-OE would be partly due to large tissue distribution, probably to the liver, based on the increased lipophilicity of the prodrug. The plasma concentrations of IM-OE and IM-BE were extremely lower than those of IM produced from the prodrugs, the plasma levels of IM-OE being slightly higher than the levels of latter. These results suggest that the ester bond of these prodrugs was rapidly hydrolyzed in plasma, although the ester bond of the lower fatty alcohol (IM-BE) showed comparatively higher affinity to enzymes, compared with that of IM-OE. The pharmacokinetic parameters obtained are shown in Table 1.

Table 1. Pharmacokinetic Parameters of IM and Its Prodrugs after i.v. Administration

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IM(a)</th>
<th>IM from IM-OE(b)</th>
<th>IM-OE</th>
<th>IM from IM-BE(a)</th>
<th>IM-BE</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (µg/ml)</td>
<td>23.8 ± 12.4</td>
<td>—</td>
<td>0.66 ± 0.52</td>
<td>10.4 ± 10.3</td>
<td>—</td>
</tr>
<tr>
<td>(µg·h/ml)</td>
<td>2.23 ± 0.52</td>
<td>—</td>
<td>6.28 ± 7.11</td>
<td>0.599 ± 0.274</td>
<td>—</td>
</tr>
<tr>
<td>β (µg/ml)</td>
<td>32.4 ± 3.0</td>
<td>—</td>
<td>0.165 ± 0.088</td>
<td>18.8 ± 8.3</td>
<td>—</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>0.108 ± 0.014</td>
<td>—</td>
<td>0.395 ± 0.144</td>
<td>0.120 ± 0.021</td>
<td>—</td>
</tr>
<tr>
<td>k10 (h⁻¹)</td>
<td>6.49 ± 0.83</td>
<td>7.25 ± 1.66</td>
<td>1.88 ± 0.69</td>
<td>5.94 ± 1.13</td>
<td>—</td>
</tr>
<tr>
<td>k12 (h⁻¹)</td>
<td>0.182 ± 0.039</td>
<td>0.099 ± 0.020</td>
<td>1.49 ± 1.15</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>k21 (h⁻¹)</td>
<td>0.760 ± 0.193</td>
<td>—</td>
<td>3.68 ± 4.74</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>AUC (µg·h/ml)</td>
<td>313 ± 27</td>
<td>52.3 ± 8.0</td>
<td>0.560 ± 0.03</td>
<td>188 ± 64</td>
<td>0.526 ± 0.345</td>
</tr>
<tr>
<td>AUMC (µg·h²/ml)</td>
<td>2849 ± 578</td>
<td>474 ± 106</td>
<td>1.16 ± 0.33</td>
<td>1513 ± 983</td>
<td>—</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>9.02 ± 1.08</td>
<td>8.98 ± 0.66</td>
<td>2.03 ± 0.47</td>
<td>7.56 ± 2.10</td>
<td>—</td>
</tr>
<tr>
<td>CI (ml/h/kg)</td>
<td>24.4 ± 2.2</td>
<td>—</td>
<td>8801 ± 459</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Vss (ml/kg)</td>
<td>219 ± 12</td>
<td>—</td>
<td>17705 ± 3229</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>V1 (ml/kg)</td>
<td>138 ± 21</td>
<td>—</td>
<td>8239 ± 6036</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Dose: a) 7.6 mg and b) 5.0 mg IM equivalent/kg. Each value represents the mean ± S.D. (n = 3–5). a) The drug plasma concentration data were fitted to a 2-compartment model or b) to a 1-compartment model. c) AUC = A/A/B/β. d) AUMC = A/A²+B/β². e) Vss = dose/ AUMC(AUC)².

Fig. 2. Plasma Concentration-Time Profiles of IM, IM-OE (A) and IM-BE (B) after i.v. Administration

Each point represents the mean ± S.D. (n = 3–5). □, IM; ■, IM from IM-OE; △, IM-OE; ○, IM from IM-BE; △, IM-BE. Dose, 7.6 mg/kg IM equivalent for IM and IM-BE and 5.0 mg/kg IM equivalent for IM-OE.

Fig. 3. Plasma Concentration-Time Profiles of IM, IM-OE (A) and IM-BE (B) after p.o. Administration

Each point represents the mean ± S.D. (n = 4–5). □, IM; ■, IM from IM-OE; △, IM-OE; ○, IM from IM-BE; △, IM-BE. Dose, 7.6 mg/kg IM equivalent.
oral administration of IM-OE was due to the high hepatic uptake. Therefore, the lower plasma levels of IM after dosing with IM-BE would partly be ascribed to the hepatic uptake, although the hepatic uptake of IM-BE seems likely to be lower than that of IM-OE, judging from the plasma levels.

The pharmacokinetic parameters are summarized in Table 2. IM-OE and IM-BE showed apparently low bioavailability (2.1 and 15.0%, respectively), compared with that (58.9%) of oral dosing of IM.

The peak levels of IM after IM-OE and IM-BE dosing appeared slightly later than that after IM dosing alone. Low levels of IM-OE and IM-BE in plasma were observed after oral administration of the prodrugs, indicating a rapid hydrolysis of the ester bond in systemic circulation.

Consequently, the pharmacokinetic behavior of IM following i.v. and oral administrations of the parent drug and prodrugs was extremely different between dosing routes; much lower plasma levels of IM produced from the prodrugs compared with those after dosing of the parent drug were due to the large hepatic distribution of IM-OE.

**Ulcereogenic Activity** Gastrointestinal damage (ulceration or hemorrhage) is a serious side effect associated with many acidic NSAIDs. IM is a potent anti-inflammatory agent, but its clinical use is strongly limited by its gastrointestinal side effects and its short half-life. To diminish the gastrointestinal damage of IM, ester prodrugs were synthesized and ulcerogenic activities were tested after repeated dosing (twice daily for 1 or 3 d) of the prodrugs. The numbers of ulcers of the stomach and intestine are shown in Fig. 4. IM was more significantly irritating to the gastrointestinal mucosa than IM-OE and IM-BE, and there were many hemorrhagic ulcers, perforations, polyps and malignant adhesions in the intestinal mucosa, especially in the jejunal mucosa, after dosing of IM for 3 d.

No ulcerogenic activity was observed in the gastrointestinal mucosa after dosing of the prodrugs twice daily for 1 d, whereas 4 ulcers were seen in the stomach after IM dosing. It is worth noting that neither of the prodrugs exerted any ulcerogenic activity on the stomach or upper intestine after repeated dosing, while slight irritation to the ileum was recognized. These results could be explained on the basis of the inhibition of both direct contact and systemic gastrotoxic effects. These also indicated that the prodrugs would be absorbed through the intestinal mucosa in the form of an ester. The slight irritation to the ileum might be due to hydrolysis of the ester bond by intestinal microorganisms, resulting in the production of the parent drug, IM, there.

### Table 2. Pharmacokinetic Parameters after Single i.v. and Oral (p.o.) Administrations of IM and Its Prodrugs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IM</th>
<th>IM</th>
<th>IM from IM-OE</th>
<th>IM-OE</th>
<th>IM from IM-BE</th>
<th>IM-BE</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (µg·h/ml)</td>
<td>313.2±27.3</td>
<td>184.4±54.7</td>
<td>6.7±1.4</td>
<td>0.3±0.2</td>
<td>47.1±11.4</td>
<td>0.6±0.5</td>
</tr>
<tr>
<td>AUMC (µg·h²/ml)</td>
<td>—</td>
<td>130.7±67.5</td>
<td>55.2±16.9</td>
<td>—</td>
<td>475.0±153.9</td>
<td>—</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>—</td>
<td>7.1±1.2</td>
<td>8.3±1.5</td>
<td>—</td>
<td>9.8±1.6</td>
<td>—</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>—</td>
<td>58.9</td>
<td>2.1</td>
<td>—</td>
<td>15.0</td>
<td>—</td>
</tr>
</tbody>
</table>

Dose: 7.6 mg IM equivalent/kg. Each value represents the mean ± S.D. (n=4–5).

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**Microsomal Drug-Metabolizing Enzyme Activities after Oral Administration** In order to clarify the effect of IM and the prodrugs on hepatic drug-metabolizing enzymes as an index of hepatic injury, microsomal P450 and aniline hydroxylase activities were determined in the dose group in comparison with the control group. As shown in Table 3, multiple treatment (six doses for 3 d) with IM significantly decreased P450 and aniline hydroxylase activities to about 20% of the control, while the treatment with IM for 1 d (two doses) did not affect the activities. On the other hand, both activities after multiple treatment with IM-OE and IM-BE were slightly but not significantly decreased compared with those of the control. These results suggest that the multiple doses of prodrugs produced less injury to the liver, in spite of the probable accumulation of prodrug in the liver. This may be explained by the prodrug accumulating in the form of an ester, without local irritation by the free carboxylic acid group, as shown in a previous paper.

Our results obtained following IM treatment agreed well data that the continued administration of IM decreased the microsomal concentration of P450 and the metabolic enzyme activities to a greater extent. It is suggested that the denaturation of P450 by NSAIDs was due to a detergent-like, membrane-perturbing action of the drugs and that in most cases the denaturation also involved a specific effect of a chlorophenyl moiety of the drug.

**In Vitro Hydrolysis of Ester Bond of Prodrugs** An essential requisite for prodrug effectiveness is its ability to readily release the parent drug after oral administration. To characterize the tissues or organs capable of hydrolyzing the ester bond of the prodrugs, hydrolytic activity
Table 3. Hepatic Microsomal Drug Metabolizing Enzyme Activities after Oral Administration of IM and Its Prodrugs

<table>
<thead>
<tr>
<th></th>
<th>1 d</th>
<th>3 d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Liver weight (g)</td>
<td>P450 (nmol/mg protein)</td>
</tr>
<tr>
<td>Control</td>
<td>5.9 ± 0.27</td>
<td>0.84 ± 0.14</td>
</tr>
<tr>
<td>IM</td>
<td>6.3 ± 0.51</td>
<td>0.91 ± 0.21</td>
</tr>
<tr>
<td>IM-OE</td>
<td>6.6 ± 0.37</td>
<td>0.89 ± 0.11</td>
</tr>
<tr>
<td>IM-BE</td>
<td>5.1 ± 0.56</td>
<td>1.01 ± 0.13</td>
</tr>
</tbody>
</table>

Each value represents the mean ± S.D. (n=4). Dose: 7.6 mg IM equivalent/kg. <sup>a</sup> p < 0.05 compared with the control.

Fig. 5. Time Course of Hydrolysis of IM-OE (A) and IM-BE in Various Tissues
Each point represents the mean ± S.D. (n=4–5). □, plasma; ●, whole blood; ○, skin; △, liver; □, small intestinal mucosa.

Table 4. Activities and First-Order Rate Constants for the Hydrolysis of IM-OE and IM-BE

<table>
<thead>
<tr>
<th>Tissue</th>
<th>IM-OE</th>
<th>IM-BE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Activity (IM µg/h/mg protein)</td>
<td>Rate constant × 10&lt;sup&gt;-1&lt;/sup&gt; (h&lt;sup&gt;-1&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Whole blood</td>
<td>0.646 ± 0.086</td>
<td>0.009 ± 0.001</td>
</tr>
<tr>
<td>Plasma</td>
<td>1.660 ± 0.221</td>
<td>0.022 ± 0.003</td>
</tr>
<tr>
<td>Liver&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.369 ± 0.065</td>
<td>0.005 ± 0.001</td>
</tr>
<tr>
<td>Skin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.871 ± 0.933</td>
<td>0.051 ± 0.012</td>
</tr>
<tr>
<td>Intestinal mucosa</td>
<td>0.275 ± 0.061</td>
<td>0.004 ± 0.001</td>
</tr>
</tbody>
</table>

<sup>a</sup> 10000 × g supernatant. Each value represents the mean ± S.D. (n=4).

was measured using whole blood, plasma, intestinal mucosa and the homogenates of liver and skin. As a result, the semilogarithmic plots of the concentrations of remaining prodrug as a function of time showed good linearity, indicating that the hydrolysis of prodrugs was adequately described by pseudo-first-order kinetics. IM-OE was relatively slowly hydrolyzed in all tissues, in which the skin and plasma had a slightly appreciable activity (Fig. 5).

Table 4 shows the hydrolastic activity and first-order rate constant in the tissues. All rate constants for IM-OE were exceedingly small or negligible, except for those in the skin and plasma. The rate constants for IM-BE were much higher than those for IM-OE, and the plasma gave the highest rate constant for IM-BE. The intestinal mucosa had negligible activities. The order of apparent activity for IM-BE, expressed by IM µg/h/mg protein, was plasma > skin > liver > whole blood > intestinal mucosa. The differences in hydrolytic rate between IM-OE and IM-BE are probably due to differences in the affinity of enzymes, in that the ester bond consisting of short-chain alcohol is metabolized more rapidly than that of the longer chain by esterases.

These results indicate that the main part of the prodrugs administered orally might not be hydrolyzed to IM in the gastrointestinal tract, the ester prodrugs themselves were absorbed through the mucosa, and the hydrolysis of the ester bond of IM-BE and IM-OE would be probably occur in systemic circulation; therefore, direct contact gastrointestinal irritation was inhibited. However, the partial involvement of the liver, due to the large hepatic blood flow (6.5 ml/min, rat) in the hydrolysis of the ester...
bond, cannot be ruled out.

Since the plasma-catalyzed hydrolysis of various esters of ibuprofen and flurbiprofen may be attributed to plasma butyrylcholinesterase, also called pseudocholinesterase, the esterase may be involved in the hydrolysis of IM-BE and IM-OE.

Esters of IM may not always be fully effective anti-inflammatory agents compared with the parent drug. The principle of esterification of IM to reduce gastric ulcerogenic activity will depend on the capacity of the particular ester to release the active drug after absorption through the gastrointestinal mucosa. Relatively rapid hydrolysis in plasma would be expected to be an effective means for the production of active drug and for reducing the gastrointestinal irritation. Therefore, IM-BE appears to be superior to IM-OE in respect to the facilitated release of the parent drug based on easy hydrolysis of the ester bond in the circulation.

In conclusion, the pharmacokinetic behavior of IM following dosing of the IM and prodrugs was dramatically different, with much lower plasma levels of IM produced from the prodrugs compared with those after IM alone. These prodrugs were mainly absorbed through the gastrointestinal mucosa in the form of an ester. The ester prodrugs were thus significantly less irritating to the gastrointestinal mucosa and liver than IM. The ester bonds of IM-BE and IM-OE were hydrolyzed mainly in the systemic circulation and were barely hydrolyzed in the intestinal tract.

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1) Jennings G. H., Gut, 6, 1—13 (1965).