Intra-articular Drug Therapy in Rheumatoid Arthritis
A Study with Indoprofen

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Summary. Six patients (4 men, 2 women) with moderate/large knee effusions due to rheumatoid arthritis (RA) were studied after receiving indoprofen, 25 mg intra-articularly and then 200 mg orally 1 week later. There was significant improvement in pain ($t=3.74$, $P<0.05$), morning stiffness ($t=2.91$, $P<0.05$) and range of movement ($t=2.52$, $P<0.05$) for at least 1 week following the intra-articular injection. The terminal phase plasma half-life after the 200 mg oral dose was $6.4 \pm 0.7$ h (mean ± SEM) and was significantly longer than the often quoted plasma half-life of 2–3 h from previous studies, but much less than the pharmacodynamic half-life. Synovial fluid concentration were not significantly different from those in plasma in the post-distribution phase. Intra-articular indoprofen may be a useful addition to the treatment of RA.

Key words: Indoprofen - Rheumatoid arthritis - Intra-articular - Oral

Introduction

Intra-articular drug administration for a particularly troublesome joint is now an established part of the overall management of rheumatoid arthritis [1]. Although the use of intra-articular corticosteroid is widely accepted, attempts have been made to use non-steroidal anti-inflammatory drugs in a similar way. These drugs have included phenylbutazone [2] and more recently aspirin [3]. Attempts with both drugs however have been thwarted. Although phenylbutazone was found to be effective, it caused a severe local reaction before taking effect [2]. This may occasionally occur with corticosteroids when given intra-articularly and have been attributed to a crystal-induced synovitis [4]. Intra-articular aspirin was found by Rylance et al. to be no better than placebo, but hydrocortisone was also ineffective [2].

Indoprofen, a non-steroidal anti-inflammatory drug and a derivative of propionic acid, has well-documented analgesic and anti-inflammatory activity in animals and humans [5]. It has been formulated for both oral and parenteral administration. The latter being buffered and completely water soluble is unlikely to cause a crystal-induced synovitis when given intra-articularly. We report here clinical and pharmacokinetic studies following intra-articular administration of indoprofen in six patients with rheumatoid knee effusions and compare the pharmacokinetics with orally administered drug.

Materials and Methods

Patients. Six patients, four males and two females, with moderate to large knee effusions due to classic or definite rheumatoid arthritis by the American Rheumatism Association criteria, were admitted into the study after giving informed consent. All the patients had normal renal and liver functions and were taking non-steroidal anti-inflammatory drugs at the time of the study. Four patients were also taking long-acting drugs including penicillamine in two, chlorambucil in one and levamisole in another. Until the time of the study, none of the patients had received indoprofen.

Indoprofen Administration. At 8 a.m. on day 1 of the study, each patient was given 25 mg indoprofen by intra-articular injection into the affected knee. One week later, each patient received a 200 mg tablet by mouth 1 h after a light breakfast. All other treatment including non-steroidal anti-inflammatory drugs were continued unchanged during the study. The patients did not fast before each dose in order to simulate the clinical situation where gastric irritation is avoided.

Clinical Assessments. Clinical assessments were made by a single observer before the intra-articular injection and repeated after 1 day, 1 week and 1 month. Assessments of the knee included the duration of morning stiffness (minutes), pain (10 cm visual analogue scale), range of motion (goniometer), tenderness (four-point scale), local temperature (four-point scale) and joint circumference (cm).

Pharmacokinetics. Paired synovial fluid and plasma samples were taken before and again 1, 2, 4, 8, 12 and 24 h after each dose of indoprofen. The samples were stored at $-20^\circ$C until assayed for indoprofen by the gas liquid chromatographic method of Tosolini et al. [6]. This method is sensitive to 0.05 µg/ml. The half-life of the drug in plasma was determined from the slope ($\beta$) of the mono-exponential curve of best fit for the terminal phase 8–24 h of the concentration-time curve using the formula:

$$T/2 = \frac{0.693}{\beta}$$
The mono-exponential curve of best fit between 8 and 24 h following the oral dose (see Fig. 2) was determined by the method of least squares using a desk top computer (Hewlett Packard, HP97). For five patients this meant only 3 data points and in the sixth patient 4 points were used to determine β. However, the correlation coefficient (r) was always > 0.99 giving a P value always < 0.01. Also the time interval was almost three times the T½. The area under the concentration-time curve to 24 h was calculated by the trapezoidal rule and extrapolated to infinity by adding the function (C_T/β) where C_T is the last measured concentration of the drug and β as defined above [7].

Statistical Analysis. The results were analysed using Students' t-test applied to paired data.

Results

The results of the clinical assessments are shown in Table 1 and Fig. 1. The duration of morning stiffness fell significantly (t=2.91, P<0.05) within 24 h and this improvement was maintained throughout the study period of 1 month. Joint circumference showed no significant change. The range of motion improved reaching a peak and statistical significance (t=2.52, P<0.05) 1 week after the intra-articular injection. Similarly, pain score also improved and reached a plateau between 1 week and 1 month (t=3.74, P<0.05). As local tenderness was evident in only two patients and local warmth in none, these parameters could not be analysed. None of the patients experienced any local reactions or any other side effects.

The mean ± SEM plasma indoprofen concentrations following the 200 mg oral dose are shown in Fig. 2. It can be seen that there is a bi-exponential fall in the concentration with time, with a slower terminal phase between 8 and 24 h. The T½ during this phase was 6.4 ± 0.7 h (mean ± SEM). In Fig. 3 a comparison is made between the simultaneous plasma and synovial fluid concentrations of indoprofen (μg/ml) in relation to time (hours) in the six patients following 200 mg indoprofen given orally. The mean peak plasma concentration was 22.0 μg/ml (range 12.1–45.4) and was reached 1–2 h after the dose. The synovial fluid concentrations, also shown in the same figure, rose steadily to reach a peak of 6.1 ± 0.8 μg/ml 4 h after the oral dose. Between 8 and 24 h the synovial fluid concentrations were not significantly different from the plasma concentrations. This was reflected in the half-life of the drug in synovial fluid, which was 6.3 ± 0.6 h and not significantly different from that in plasma.

Figure 4 shows the mean (± SEM) concentrations of indoprofen in synovial fluid and plasma in the same six patients following the intra-articular injection of 25 mg indoprofen. The synovial fluid concentrations this time

Table 1. Results of clinical assessments following 25 mg indoprofen given intra-articularly

<table>
<thead>
<tr>
<th>Parameter measured</th>
<th>Before indoprofen</th>
<th>24 h</th>
<th>1 week</th>
<th>1 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning stiffness</td>
<td>38.3±13.6</td>
<td>15.0±5.5*</td>
<td>20.8±9.0*</td>
<td>10.0±5.2*</td>
</tr>
<tr>
<td>(min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint circumference</td>
<td>37.3±0.8</td>
<td>36.9±1.0</td>
<td>36.7±0.8</td>
<td>37.3±0.9</td>
</tr>
<tr>
<td>(cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range of motion</td>
<td>113.3±8.9</td>
<td>129.2±6.6</td>
<td>135.8±3.3*</td>
<td>134.2±4.9*</td>
</tr>
<tr>
<td>(degrees)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain (mm)</td>
<td>52.0±13.0</td>
<td>26.0±9.6</td>
<td>17.5±8.9**</td>
<td>15.0±7.0**</td>
</tr>
</tbody>
</table>

* P<0.05; ** P<0.025. Values given are mean ± SEM

Fig. 1. Results of clinical assessments in relation to time following intra-articular indoprofen (*P < 0.05; **P < 0.025). Values given are mean ± SEM