

## PERCUTANEOUS ADMINISTRATION OF INDOMETHACIN IN RHEUMATOID ARTHRITIS

### Evaluation of Two Topical Preparations

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#### ABSTRACT

A comparative open crossover clinical study of topical indomethacin administered either as a spray or gel was performed in 20 patients with rheumatoid arthritis, as well as a study of penetration from the indomethacin spray alone in synovial fluid of the knee in three other patients. The study demonstrated that indomethacin spray was as effective as indomethacin gel in reducing proximal interphalangeal (PIP) joint diameter in rheumatoid arthritis. Except for local discomfort in two (10%) of the patients in each group, both products were very well tolerated. Indomethacin applied as a topical spray was shown to penetrate into knee joint synovial fluid in the three other patients studied.

#### INTRODUCTION

Indomethacin (a 3-indolyl-acetic acid derivative) is a commonly used anti-inflammatory drug. In recent years, there have been many trials concerning the development of dermal and transdermal delivery systems of anti-inflammatory compounds in order to avoid the systemic side effects after oral or parenteral administration.<sup>1-3</sup> Only limited data that includes both the evaluation of penetration and clinical efficacy of topically applied indomethacin is currently available.<sup>1,3-5</sup>

The purpose of this study was to evaluate the effect of two topical indomethacin preparations on the diameter of proximal interphalangeal (PIP) joints, flexion-induced pain, pressure-induced pain, and pain scores on a 10-cm linear scale in rheumatoid arthritis patients. Furthermore, plasma and synovial indomethacin levels were assayed after percutaneous application of the indomethacin spray in three other patients with rheumatoid arthritis.

#### MATERIALS AND METHODS

Twenty patients with definite rheumatoid arthritis<sup>6</sup> entered the study

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after giving oral informed consent. All patients had at least one painful PIP joint reflecting rheumatic involvement. Three other patients with rheumatoid arthritis were included for assay of synovial and plasma indomethacin levels after topical application of indomethacin spray. None of the patients had previously received indomethacin and there had been no changes in their treatments for at least the last six months.

Two topical indomethacin preparations were investigated: a commercially available indomethacin gel\* containing 1% indomethacin and a spray† containing 4% indomethacin in an alcoholic solution.

An open randomized crossover study was carried out in 20 patients. The patients were randomly divided into two therapeutic groups. The first group received the gel (100 mg/day in three applications) and the second the spray (100 mg or 2.5 ml/day in three applications) on the involved joints for one week. The different clinical parameters were evaluated at 8 AM, before and after one week of treatment. During the following week, the patients then received the other drug under identical conditions. Two patients dropped out of the study without any explanation, after the first (patient 10) and second (patient 20) office visits, respectively.

In three other patients with rheumatoid synovitis of the knee, 100 mg of indomethacin spray was applied to the involved knee, and a 10-ml synovial fluid sample was aspirated three hours later.

Serum indomethacin levels were assayed before application of the spray and serum and synovial indomethacin levels were assayed at the time of arthrocentesis.

### *Indomethacin Assay*

An automated high performance liquid chromatographic method was used for indomethacin assay of plasma and synovial fluid samples.

The sample (100  $\mu$ l) was injected directly into the chromatographic system; the cleanup step was performed by a column-switching technique. The precolumn used for sample cleanup and enrichment consisted of a Macherey-Nagel cartridge (Macherey Nagel GmbH & Co. KG, Duren, Federal Republic of Germany) (30 mm long  $\times$  4 mm internal diameter [ID]) filled with Vydac 201 SC (bead diameter: 30–40  $\mu$ m) and equipped with filters of 20- $\mu$ m porosity.

After sample injection, the precolumn was washed for four minutes with phosphate buffer pH 5.0, delivered by a Gilson model 302 pump (Gilson Medical Electronics S.A., Villiers-le-Bel, France) at a flow rate of 0.25 ml/min.

\* Trademark: Indocid® gel (Merck Sharpe & Dohme, Brussels, Belgium).

† Trademark: Dolcidium® spray (Galephar S.A., Brussels, Belgium).

An air-actuated two-position valve (Valco Instruments, Houston, Texas) was then automatically switched by an Altex model 420 microprocessor (Altex Scientific Inc., Berkeley, California) in order to connect the precolumn to the analytical column. The compounds retained on the precolumn were eluted by mobile phase consisting of phosphate buffer pH 3.0 and methanol (1:3). Mobile phase was pumped by a model 6000 A Waters Associates pump (Milford, Massachusetts) at a flow rate of 0.7 ml/min.

Eluted compounds were separated with the same mobile phase on the analytical reversed-phase column (250 mm long  $\times$  4 mm ID) containing Nucleosil C6H5 (particle diameter: 7  $\mu$ m, Macherey-Nagel). Indomethacin was first monitored photometrically at 254 nm by a Waters model 440 absorbance detector and then fluorometrically, after hydrolysis by sodium hydroxide in a postcolumn reactor by a Varian Associates fluorichrom detector (Walnut Creek, California) equipped with a deuterium lamp. Excitation and emission wavelengths were 220 nm and 370 nm, respectively. The postcolumn reactor consisted of knitted teflon tubing (3,050 mm long  $\times$  0.5 mm ID) immersed in a waterbath at 60 °C.

0.1 N sodium hydroxide was injected in the column effluent at a flow rate of 0.4 ml/min by a second Gilson pump, equipped with a model 802 manometric model. Nine minutes after sample injection, the valve was switched back to its original position and the precolumn was thus filled with washing eluent. One minute later, the next sample was injected and a new cycle was started.

The absolute recovery of indomethacin was 95% and limit of detection was 10 ng/ml. Coefficients of variation of 2.2% to 3.2% (intratest) and 3.6% to 3.7% (intertest) were found in a sample containing 250 ng of indomethacin per ml.

### *Statistical Analysis*

The Wilcoxon rank test was used to compare values for each preparation before and after treatment of joint diameters, flexion-induced pain scores, pressure-induced pain scores, and pain scores on a 10-cm linear scale.

The chi-square test compared the efficacies of the two treatments.

## RESULTS

Clinical status of patients after topical application of both indomethacin preparations was significantly improved (see the figure). Statistical comparison of objective measurements of PIP joint diameters before and after treatment demonstrated a significant reduction in joint swelling for both

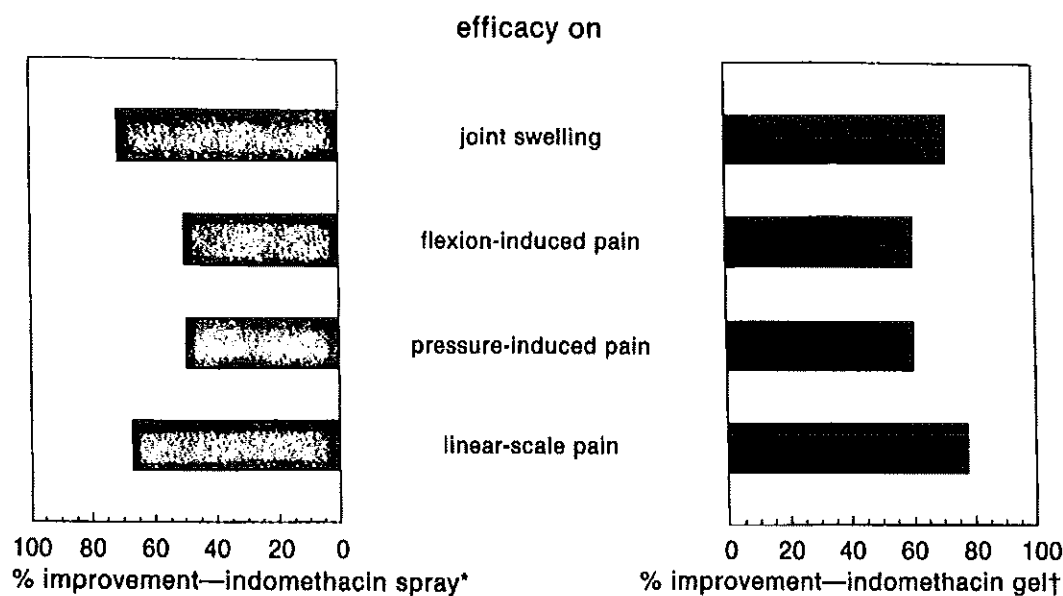


Figure. Comparison of the efficacy of two topical indomethacin preparations on objective and subjective clinical parameters. \*Trademark: Dolcidium® spray (Galephar S.A., Brussels, Belgium) †Trademark: Indocid® gel (Merck Sharpe & Dohme, Brussels, Belgium)

the indomethacin gel ( $P < 0.01$ ) and the indomethacin spray ( $P < 0.05$ ) preparations.

Statistical comparison of subjective patient scores for flexion-induced pain, pressure-induced pain, and pain scores on a 10-cm linear scale generally demonstrated significant improvement for both the indomethacin gel ( $P < 0.01$ ) and the indomethacin spray ( $P < 0.01$ ) preparations.

Moreover, the percentage of improvement in clinical status of patients was not significantly different for the two tested preparations (chi-square: not significant). Two patients in each group discontinued treatment because of local discomfort. No cutaneous changes or systemic side effects were reported.

Pharmacokinetic data in the three patients with rheumatoid synovitis of the knee showed that serum indomethacin levels were not detectable before application of 100 mg (2.5 ml) of indomethacin spray on the involved knee joint. Three hours after application of the spray, indomethacin synovial levels were 20, 25, and 60 ng/ml, respectively, in the three subjects, while serum levels remained virtually undetectable.

#### DISCUSSION AND CONCLUSIONS

Synovial levels of indomethacin reported after topical administration of 100-mg indomethacin spray were far lower than those obtained after oral administration of 50 mg of indomethacin, for which the maximum synovial

levels reached  $700 \pm 240$  ng/ml.<sup>7</sup> However, this peak was reached two hours after oral intake, and no data currently available concerning the pharmacokinetics of percutaneous administration of indomethacin on the knee of rheumatoid arthritis patients. Since plasma peaks of indomethacin following application of gel on the skin of the back<sup>5</sup> were delayed from one to two hours compared with the peak reported after oral intake, we expected the synovial peak after percutaneous administration to also be delayed. Even if synovial levels of indomethacin following percutaneous application of the indomethacin spray were low, they confirm the penetration of indomethacin through the joint by this route of administration. No data currently exist on the minimal synovial concentration of indomethacin required to induce a local anti-inflammatory effect.

However, under our experimental conditions, the two tested topical indomethacin preparations induced a significant reduction in PIP joint diameter. This is in accordance with the anti-inflammatory activity of topically applied indomethacin previously reported in animal models.<sup>1</sup> Local tolerance was excellent for the two preparations and no systemic side effects were encountered.

We therefore conclude from these results that both the indomethacin spray and gel preparations are effective and nontoxic in the treatment of localized rheumatic disorders. There was no significant difference in clinical activity of the two preparations. Identical clinical efficacy was demonstrated for both tested preparations.

The indomethacin spray is easy to use and significantly improves local symptoms of rheumatoid arthritis in patients with limited and/or painful movement of affected joints. Because significant plasma levels of indomethacin are not reached, the risk of systemic side effects related to the use of this active ingredient may be substantially reduced.

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