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# Comparison of serum indomethacin profiles after rectal administration of two brands of indomethacin suppositories in healthy volunteer subjects

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**Summary**

Previous in vitro dissolution data indicated a much slower release of indomethacin from Indocid suppositories than from Imbrilon suppositories; both products contain 100 mg of indomethacin. Since in vitro findings require in vivo validation before clinical recommendations can be made, the present study was designed to compare the in vivo release characteristics of the two products. The study was carried out in 12 volunteer subjects in a fully randomized double-blind cross-over fashion and involved administration of Indocid and Imbrilon suppositories at bedtime. Venous blood samples were obtained over the first 12 h post-drug administration, while pooled urine was collected from 0–12 and 12–24 h. Indomethacin content of all samples were measured using HPLC. The experimental data were compared using the following parameters: $T_{max}$, $C_{p_{max}}$ and all other timed plasma concentrations, $AUC_{0\text{-}12h}$ and cumulative urinary excretion data from 0–12, 12–24 and 0–24 h. Statistical analyses, using the paired *t*-test, indicated that no statistically significant differences ($P > 0.05$) occurred between any of the measured parameters for the two products. It is therefore unlikely that clinically significant differences between the two products will be seen during treatment in patients.

## Introduction

Indomethacin is a potent non-steroidal anti-inflammatory agent indicated for the treatment of pain and moderate to severe inflammation in rheumatic disease and other acute musculoskeletal disorders. The drug is available as both solid and liquid preparations for oral administration and as a suppository formulation for rectal administration. Suppositories are usually given at bedtime in an attempt to relieve the symptoms of early morning stiffness without producing undue gastric upset. Holt and Hawkins (1965), observed that indomethacin given as a suppository often has a larger lasting clinical effect than when the same dose is given by mouth. These findings, however, were not supported by Baber et al. (1980) who found no significant differences in clinical assessments between the two routes of administration. Clearly, however, the clinical efficacy of a fixed dose suppository product in relieving early morning stiffness may be formulation-dependent, i.e. if

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a particular product releases its drug more slowly, it is more likely to give rise to relief of early morning symptoms.

In a recent in vitro study (McElnay and Nicol, 1984) using a USP-NF rotating basket and a continuous-flow bead-bed dissolution apparatus described by Roseman et al. (1981) it was shown that two popular brands of indomethacin suppositories used clinically in the United Kingdom, (Indocid and Imbrilon) had quite different in vitro drug release characteristics.

Both types of apparatus yielded a much slower indomethacin release pattern in the case of the Merck Sharpe and Dohme preparation (Indocid). Difficulties have been experienced in the past, however, in extrapolating in vitro indomethacin data to the in vivo situation (Rowe and Carless, 1981). The aim of the present investigation was therefore, to compare the serum profiles of indomethacin after rectal administration of Indocid and Imbrilon suppositories to healthy volunteer subjects, since major differences in the rate of drug release can have important implications for clinical practice.

## Methods

*Subjects*

Twelve healthy volunteers (9 males and 3 females; mean age $24.2 \pm 1.2$ years) entered into the study protocol which was approved by the university ethical committee. Each subject underwent a full medical examination (including full blood analysis) before being considered for entry into the study. Volunteers gave full informed consent and were free to withdraw from the study at any time. Only volunteers who were not taking any chronic drug therapy (including oral contraceptives) were chosen and all subjects were asked to refrain from taking any casual drug therapies e.g. analgesics, cough and cold preparations and alcoholic beverages for 3 days before and during the study periods.

*Study protocol*

The trial was carried out in a fully randomized double-blind cross-over fashion and consisted of two treatment periods at least 7 days apart. An example of the treatment schedule for one volunteer is as follows. In the first treatment period an Indocid suppository (indomethacin 100 mg) was administered to the volunteer at 21.00–22.00 h and the volunteer went to bed. Blood samples (10 ml) were taken via an indwelling butterfly cannula just prior to the insertion of the suppository and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10 and 12 h post-administration. After each blood sample was taken the cannula was flushed with heparinized saline (50 units/ml) to maintain patency. When possible the volunteer was not aroused from sleep during sampling. Each blood sample was immediately transferred into a heparinized tube. Urine was also collected and pooled from 0–12 and from 12–24 h. The separated plasma and urine samples were stored at $-20°C$ until assay for indomethacin content was carried out. In the second treatment period the complete procedure was repeated with the Indocid suppository being replaced with an Imbrilon suppository (indomethacin 100 mg).

*Determination of indomethacin in plasma and urine samples*

Indomethacin was assayed in plasma and urine samples using a sensitive specific high pressure liquid chromatography (HPLC) method. The chromatographic conditions were based on those used by Skellern and Salole (1975) while sample preparation was based on the work of Lin and Benet (1977). In order to precipitate plasma proteins an aliquot of acetonitrile (0.8 ml) was added to an aliquot of each plasma sample (0.4 ml). The mixture was vortexed for 30 s and centrifuged for 10 min at 4000 *g*. The acetonitrile contained mefenamic acid (1 $\mu$g/ml), the internal standard used in the present assay. A portion of the supernatant (100 $\mu$l) was injected on to the column which was 15 cm $\times$ 4.6 mm stainless steel packed with Hypersil ODS (5 $\mu$m particle size). An ODS guard column was also used to protect the analytical column. The mobile phase consisted of 30%, 0.1 M sodium acetate, adjusted to pH 3.2 with glacial acetic acid, and 70% methanol. A flow rate of 2 ml $\cdot$ min$^{-1}$ was utilized. Integrated peak areas were measured at $\lambda = 254$ nm and the peak

area ratio method was utilized for the estimation of unknown sample concentrations by reference to a standard calibration curve. Urine samples were spiked with internal standard and aliquots (100 $\mu$l) injected directly on to the column. The assay method was found to be reproducible with a correlation coefficient over the concentration range 0–5 $\mu g \cdot ml^{-1}$ of 0.9998 and a coefficient of variation for 10 plasma samples (each containing 0.625 $\mu g \cdot ml^{-1}$) of 0.0366.

*Interpretation of results*

The experimental data were compared using the following criteria:

(i) $T_{max}$ = time taken to reach maximum plasma concentration;

(ii) $C_{P_{max}}$ = maximum recorded plasma concentration and all other timed plasma concentrations;

(iii) $AUC_{0\text{-}12h}$ = area under the plasma concentration time curve between zero time and twelve hours. (These areas were measured using the trapezoidal method);

(iv) urinary indomethacin excretion from 0–12, 12–24 and 0–24 h.

All experimental data for the two formulations were compared statistically using the paired *t*-test. In an attempt to ascertain if sex differences contributed to the variability in kinetic parameters data were compared separately for males and females ($n = 12$) and for males alone ($n = 9$).

## Results and Discussion

All subjects tolerated the procedures well and all retained the suppositories after first placement.

The plasma profiles for the two treatments are shown in Figs. 1 and 2. The plasma profile data obtained after administration of the two different products are summarized in Table 1 together with the results for statistical analyses. All data fell within the expected normal values for indomethacin (Alvan et al., 1975). It is clear from Figs. 1 and 2 and the statistical results that there was no significant difference between the treatments both when data were compared separately for males and females ($n = 12$) or for males alone ($n = 9$). Although not tabulated there were no significant differences ($P > 0.05$) between the plasma concentrations at any sampling time for the two products. Urinary excretion data are presented in Table 2. As with the plasma data no statistical differences ($P > 0.05$) between treatments were found for the urinary excretion of indomethacin.

There were, however, trends within the data in the time taken ($T_{max}$) to reach maximal serum concentrations ($C_{P_{max}}$). As predicted from in vitro findings (McElnay and Nicol, 1984), the time taken to attain maximal plasma concentrations was

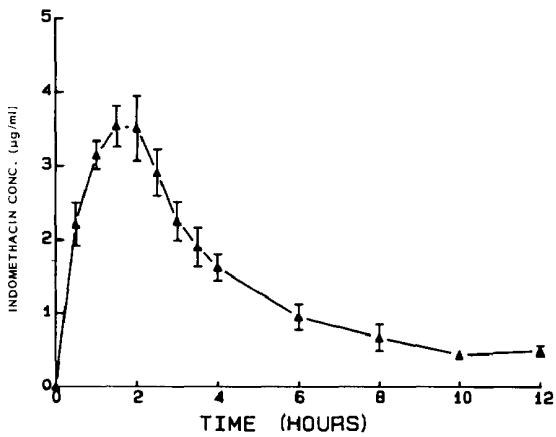


Fig. 1. Serum profile for indomethacin in 12 volunteers after administration of an Indocid suppository at bedtime. (Each point represents the mean ± S.E., $n = 12$.)

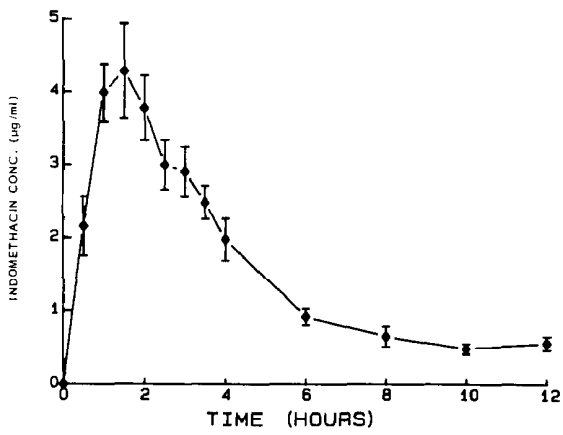


Fig. 2. Serum profile for indomethacin in 12 volunteers after administration of an Imbrilon suppository at bedtime. (Each point represents the mean ± S.E., $n = 12$.)

TABLE 1

SUMMARY OF SERUM PROFILE DATA (MEAN ± S.E.) OBTAINED AFTER NIGHT-TIME ADMINISTRATION OF INDOCID AND IMBRILON® SUPPOSITORIES ($n$ = 12)

| Product administered | AUC ($\mu$g/ml·min) | $T_{max}$ (h) | $C_{P_{max}}$ ($\mu$g/ml) |
|---|---|---|---|
| Indocid | 986.81 ± 78.89 | 1.75 ± 0.16 | 4.25 ± 0.36 |
| Imbrilon | 1112.37 ± 104.36 | 1.42 ± 0.17 | 5.19 ± 0.59 |
| T [a] | 1.07 | 1.20 | 1.54 |
| $P$ | > 0.05 | > 0.05 | > 0.05 |

Data were also compared for males alone ($n$ = 9). Again no significant differences ($P > 0.05$) were found between the treatments.

[a] T value required for significance at the $P = 0.05$ level = 2.20.

greater with the Indocid suppositories (see Table 1), although this fact is somewhat obscured in Figs. 1 and 2 in which plasma data from all 12 volunteers was averaged for each sample time. Clearly the difference was much less marked in vivo than might have been predicted from in vitro findings and the result is unlikely to lead to clinically significant differences between the two products. A similar picture of in vitro but not in vivo differences in indomethacin release has been described for a conventional formulation and a commercially available sustained release indomethacin product (Indocid, 75 mg; Rowe and Carless, 1981).

There was a wide variation in urinary excretion data between subjects; however, the mean data indicated that approximately 10% of the indomethacin was eliminated unchanged in all cases. This agrees with previous work which showed that 10–20% of the drug is excreted unchanged in the urine by both glomerular filtration and tubular secretion (Kwan et al., 1976).

A more rapid release of indomethacin from the Imbrilon suppositories may have been responsible for the increased $C_{P_{max}}$ and AUC values recorded for this product (Table 1). Again the differences are unlikely to be of clinical significance.

The present study involved 12 volunteers of a narrow age range under strictly controlled conditions. Even with this relatively large number of subjects for a clinical trial of this nature, the standard error values within individual results were relatively high, indicating a relatively large inter- and intra-subject variation in both the plasma levels achieved and the urinary excretion of indomethacin. Variations in response should therefore be expected in the clinical setting when both the timing of administration and physical activity after administration will vary more widely, as will the age and weight of the patients. Although this latter problem should be borne in mind during clinical assessment of patients receiving rectal indomethacin the main conclusion of the present work is also of importance, i.e. since no marked differences occurred between data obtained using the two suppository products, any trends within the results are unlikely to lead to clinically important differences between the products. The study also highlights the problem of the extrapolation of in vitro data to the clinical setting.

TABLE 2

SUMMARY OF URINARY EXCRETION DATA OBTAINED AFTER NIGHT-TIME ADMINISTRATION OF INDOCID AND IMBRILON SUPPOSITORIES ($n$ = 12)

| Product administered | Urinary excretion of indomethacin | | |
|---|---|---|---|
| | 0–12 h ($\mu$g) | 12–24 h ($\mu$g) | 0–24 h ($\mu$g) |
| Indocid | 8365.08 ± 990.76 | 2682.65 ± 940.24 | 11047.25 ± 1557.39 |
| Imbrilon | 6947.85 ± 795.61 | 1151.57 ± 113.70 | 8099.40 ± 851.51 |
| T [a] | 0.79 | 1.61 | 1.63 |
| $P$ | > 0.05 | > 0.05 | > 0.05 |

Data were also compared for males alone ($n$ = 9). Again no significant differences ($P > 0.05$) were found between the treatments.

[a] T value required for significance at the $P = 0.05$ level = 2.20.

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