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Bioavailability of controlled release indomethacin microspheres and pellets

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Summary

The plasma and urinary pharmacokinetics of controlled release indomethacin microsphere and pellet formulations have been compared after repeated oral administration. Statistical analysis, using the one-tailed independent mean sample *t*-test, indicated that the microsphere formulation exhibited a trend for greater relative systematic availability ($0.25 > P > 0.20$) and showed a longer time to reach maximum plasma concentration (t_{max}) than the pellet formulation ($P < 0.005$).

Indomethacin is an important non-steroidal anti-inflammatory drug with extremely variable half-life in plasma, between 2 and 16 h (O'Brien et al., 1984; Flower et al., 1985). Therefore, dosage regimens involving conventional oral dosage forms require drug administration three or four times daily, to maintain adequate therapeutic effectiveness, with the inherent problems associated with patient compliance. Additionally, the conventional dosage forms do not protect patients against morning joint stiffness which is common in rheumatoid disease states. Thus the development and clinical use of sustained or controlled release dosage forms of indomethacin may have several advantages over the use of conventional capsule formulations, e.g. reduction of the side effect, prolongation of drug action and improvement of bioavailability and patient compliance (Rowe and Carless, 1981).

The controlled release indomethacin dosage forms that have been proposed until now can be divided into single-unit and multiple-unit formulations. The multiple-units offer some very distinct advantages compared to the single-unit formulations and can be classified into pellets and microspheres (Bechgaard and Christensen, 1988). Pellets are coated units in the range of 0.3–2 mm, with the drug in a reservoir in the core. Microspheres are monolithic devices of drugs in a matrix consisting of polymers or waxes and have smaller size, larger surface area and more retarding effect of the matrix constituent. These differences in the physical properties and possibly the bioadhesiveness of microspheres may affect the G.I. transit and cause differences in the in vivo behaviour. The aim of the present investigation was to compare the pharmacokinetics (plasma levels, bioavailability and degree of fluctuations) of in-

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domethacin administered as controlled release pellets and microspheres.

The pellet type formulation was the only one commercially available in Greece and the microsphere type formulation was one amongst a series prepared experimentally, with Eudragit RS and RL polymers in equal quantities and 56.3% w/w indomethacin content, by employing an o/w emulsion solvent-diffusion technique (Malamataris and Avgerinos, 1990). The two formulations were almost equivalent as far as the in vitro dissolution behaviour is concerned (Fig. 1).

Twelve healthy volunteers (all males; mean age 21.5 ± 1.5 years) participated in the study and gave written informed consent. Each subject underwent a full medical examination (including full blood analysis) before being considered for entry into the study. None of the subjects received any other medication for at least 2 weeks prior to dosing; alcohol or caffeine containing beverages were not permitted during the 24 h period preceding and for the duration of each study period. All subjects consumed a light breakfast on the day of the trials consisting of toast and fruit juice.

The trial consisted of three treatment periods at least 7 days apart and each volunteer received the following drug dosage regimens: (a) Conventional 25 mg capsules in 3 doses of 2 capsules each at 6-h intervals ($3 \times (2 \times 25)$ mg); (b) controlled release pellets in 2 doses at 12-h intervals (2×75 mg); (c) controlled release microspheres in 2 doses at 12-h intervals (2×75 mg). The trial was carried out in a fully randomized crossover fashion.

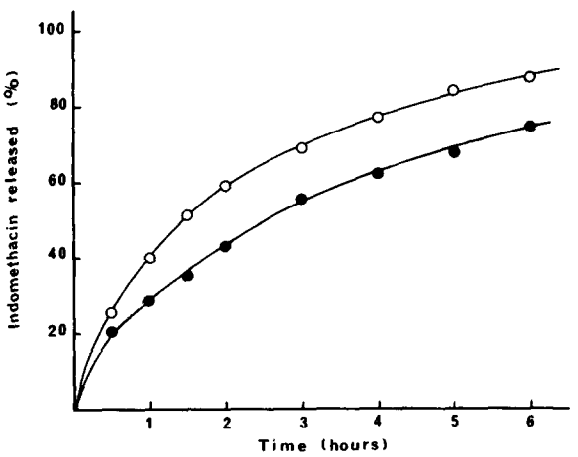

Fig. 1. In vitro dissolution profiles of indomethacin from microspheres (●) and pellets (○), in pH 6.5 phosphate buffer.

A total of 18 samples (10 ml) were withdrawn by venepuncture from each of the volunteers during the 32 h post drug administration. Each blood sample was collected in heparinized tubes and then immediately separated by centrifugation. Urine was also collected for 32 h. The volume and pH were noted and an aliquot was stored. The separated plasma and urine samples were stored at $-20\,^{\circ}C$ until assay of indomethacin content was carried out.

The plasma and urine concentrations of indomethacin were determined by a high-performance liquid chromatographic method, via a simple procedure (solvent-demixing), using a reverse-phase system and phenacetin as internal standard (Avgerinos and Malamataris, 1989). The concentration of indomethacin in urine was determined after treatment of urine samples with HCl to hydrolyse the ester glucuronide.

For comparison of the experimental data, the following pharmacokinetic parameters were calculated (Gibaldi and Perrier, 1982): Maximum recorded plasma concentration (C_{pmax}); time taken to reach maximum plasma concentration (t_{max}); apparent elimination half-life ($t_{1/2}$) from the post-absorptive phase of the plots of log plasma concentration vs time; area under the plasma concentration-time curve between zero time and the last data collection time (AUC_{0-t}). These areas were measured using the trapezoidal method and $AUC_{0-\infty}$ was calculated from the sum of AUC_{0-t} and the last observed plasma concentration divided by the elimination rate constant. The total urinary indomethacin recovery, both free and conjugated, was calculated as % dose. All experimental data were compared statistically using the one-tailed independent sample means t-test (Smith and Stewart, 1981).

The mean plasma concentration vs time curves, following the repeated oral administration of the two controlled release and the conventional capsule formulations, are shown in Fig. 2A–C. The values of the pharmacokinetic parameters calculated from the individual subject plasma profile data are summarized in Table 1 together with the results of the statistical analyses.

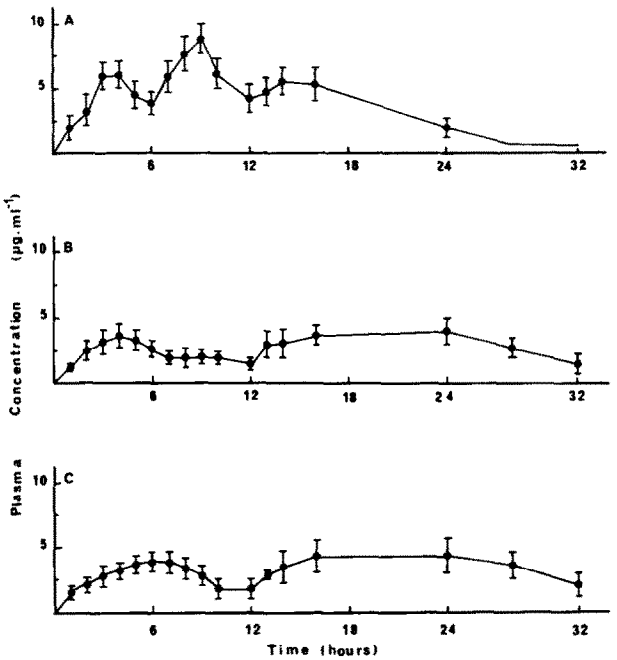

Fig. 2. Plasma profiles for indomethacin in 12 volunteers after repeated oral administration of (A) hard capsules (3×(2×25) mg), (B) pellets (2×75 mg) and (C) microspheres (2×75 mg). Results expressed as means ± S.D.

From Table 1 and Fig. 2A–C, one observes that the two controlled formulations, as expected, show lower maximum plasma concentrations (C_{pmax}), longer time to reach the maximum plasma concentration (t_{max}), longer apparent plasma elimination half-life ($t_{1/2}$) and reduced fluctuations of the plasma concentrations. All these effects are probably due to dissolution rate limited drug release and hence absorption.

The mean plasma concentrations on the morning of the second day of the study ($t = 24$ h) for the pellets and microspheres were double that after the administration of the conventional capsule formulation. The reduced fluctuations (peak-to-trough ratios) combined with the elevated mean plasma concentration on the morning of the second day of the study should be of particular importance in the therapeutic use of the controlled release dosage forms of indomethacin. It must offer advantages in the protection of the patient against morning joint stiffness.

In the urinary excretion data there was a wide variation between subjects. However, the mean data indicated that over 32 h approx. 25% of the indomethacin was eliminated as total (unchanged and conjugated) indomethacin. This is in agreement with previous reports (Flower et al., 1985) and suggests that the controlled release preparations have little effect, if any, on the ultimate metabolic fate of the drug.

On statistical comparison of the pharmacokinetic data of the microspheres and pellets, by using the one-tailed independent mean sample t-test, it was found that the microspheres had greater t_{max} ($P < 0.005$), and shorter elimination half-life ($P < 0.05$).

TABLE 1

Summary of pharmacokinetic data in 12 volunteers after repeated oral administration of controlled release indomethacin microspheres, pellets and conventional hard capsule formulation

	Microspheres			Pellets		Capsules
	Mean ± S.D.	t-test		Mean ± S.D.	t-test	Mean ± S.D.
		Capsules (T^a, P)	Pellets (T^a, P)		Capsules (T^a, P)	
C_{pmax} (μg ml^{-1})	3.2 ± 0.5	7.3, < 0.005	0.5, < 0.40	3.1 ± 0.4	7.6, < 0.005	6.9 ± 1.6
t_{max} (h)	5.8 ± 0.6	15.2, < 0.005	9.7, < 0.005	4.0 ± 0.1	331.6, < 0.005	3.0 ± 0.1
$t_{1/2}$ (h)	8.2 ± 1.8	8.6, < 0.005	2.0, < 0.05	10.4 ± 3.1	7.4, < 0.005	3.5 ± 0.1
AUC_{0-32} (μg ml^{-1} h)	104.6 ± 24.7	1.0, < 0.20	1.0, < 0.20	93.8 ± 22.8	2.3, < 0.025	114.2 ± 19.6
AUC ratio (%)	94.6 ± 28.9	0.6, < 0.30	0.8, < 0.25	84.8 ± 26.5	1.9, < 0.05	100
Urinary recovery (% dose)	22.3 ± 6.5	1.3, < 0.20	0.8, < 0.25	20.2 ± 6.1	1.9, < 0.05	26.8 ± 9.9

[a] T values required for significance at the $P = 0.05$ level = 1.72.

The systematic availability of indomethacin, as determined by comparison of the area under the plasma concentration-time curves (AUCs), is lower for both the controlled release formulations (Table 1). It is known that indomethacin is a drug which is largely converted to inactive metabolites undergoing enterohepatic circulation to varying degrees. Unchanged indomethacin (**I**), *O*-desmethyl-indomethacin (DMI) and *N*-deschlorobenzoyl-indomethacin (DBI) are the major components in plasma. Approx. 50% of an intravenous dose undergoes enterohepatic circulation as **I** and its systematic circulation can be extremely variable and may even exceed the administered dose. On average, the reported bioavailability of orally and rectally administered indomethacin is 100 and 80% relative to an intravenous reference dose (O'Brien et al., 1984). Therefore, the slower in vitro release of indomethacin from the controlled release formulations may be responsible for the decreased AUC values recorded for the controlled release products.

As far as comparison of the two controlled release formulations is concerned, the statistical analysis (Table 1) indicated that the microspheres exhibited not only a smaller and non-significant reduction in the AUC values, but also a trend for greater relative systematic availability than the pellets. This trend may be attributed to prolongation of the residence time of microspheres in the stomach. Since microspheres contain Eudragit, which strongly adsorbs polysaccharide derivatives (Kawashima et al., 1989), they may interact with mucosubstances on the surface of the stomach, leading to an improvement in bioavailability.

Nevertheless, if we take into account the narrow age range of the 12 volunteers, the strictly controlled conditions of the study and a maximum probability value (P) of 0.05 or less to consider the differences as significant, we may conclude that the trend for greater systematic availability within the results of the present study ($0.25 > P > 0.20$), is unlikely to lead to clinically important differences between the two controlled release products.

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