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BIOAVAILABILITY OF DIRECTLY-COMPRESSED INDOMETHACIN, INDOMETHACIN SODIUM AND INDOMETHACIN MEGLUMINE TABLETS

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ABSTRACT

The prepared film-coated directly-compressed indomethacin, indomethacin sodium and indomethacin meglumine tablets, plain indomethacin in hard gelatin capsule and the commercial product "Indocid"capsules, were subjected to bioavailability testing in six healthy volunteers. Each treatment was given as single oral dose of 50 mg. The excreted drug was estimated in urine at 1, 2, 4, 6, 8, 10, 12 and 24 hours post-drug administration. The cumulative amount excreted, percent dose excreted, Q_{max}, t_{max}, K_{el}, $t_{\frac{1}{2}el}$ and relative bioavailability, to plain drug, were determined. The obtained results revealed that directly-compressed film-coated indomethacin meglumine tablets had the best relative bioavailability than the other treatments.

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INTRODUCTION

Only recently have the pharmacokinetic characteristics of non-steriodal anti-inflammatory drugs been recognized as decisive factors in understanding the effects and side effects of these drugs[1]. Osol et al.[2] reported that virtually all of indomethacin administered is excreted in urine within 24 hours in man. Conjugation of indomethacin in man with glucuronic acid occurs primarily in the kidney[3]. Hucker et al.[4] reported that incubation of indomethacin glucuronide at 37°C and at pH 3-7 results in its conversion to indomethacin.

The authors[5] previously prepared film-coated directly-compressed tablets of indomethacin and its sodium and meglumine salts using the same tablet excipients and assessed their stability. In this study, the prepared tablets, plain indomethacin in hard gelatin capsule and the commercial product "Indocid" capsule were subjected to bioavailability testing on humans.

EXPERIMENTAL

Materials

Indomethacin (supplied by Misr Co., Cairo, Egypt), Indomethacin sodium (supplied by EIPICO Co., 10th of Ramadan, Egypt), Indomethacin meglumine (supplied by El-Nile Pharm. Chem. Co., Cairo, Egypt) and "Indocid" 25 mg capsules (Merk Sharp and Dohme product). All other chemicals were of analytical grade.

Treatments

The following five treatments were tested: (1) a hard gelatin capsule contains 50 mg of plain indomethacin powder (standard capsule), (2) two capsules of MSD product (Indocid 25 mg capsule), (3) two prepared and coated indomethacin tablets (indomethacin; 7.0 parts, Compactrol; 85.0 parts, Ac-Di-Sol; 2.0 parts, talc; 4.5

parts and Aerosil 200; 1.5 parts), (4) two prepared and coated indomethacin sodium tablets (indomethacin sodium; 8.5 parts, Compactrol; 80.5 parts, Ac-Di-Sol; 2.0 parts, talc; 6.5 parts and Aerosil 200; 2.5 parts) and (5) two prepared and coated indomethacin meglumine tablets (indomethacin meglumine; 10.5 parts, Compactrol; 77.0 parts, Ac-Di-Sol; 2.0 parts, talc; 6.0 parts and Aerosil 200; 4.5 parts).

Human Subjects

Six healthy young male adult volunteers were fully informed and cautioned to avoid any medication for one week preceding the study. Their ages ranged from 26 to 30 years, and body weight from 60 to 82 kg.

Design

The design corresponded to an open randomized five-way crossover pilot study. The subjects were fasted overnight before each treatment and no food was allowed at least for four hours after dosing. On the morning of the treatment, each subject drank 200 ml of water at least one hour before dosing and after each urine collection. Complete urine collections were made at intervals of 1, 2, 4, 6, 8, 10, 12 and 24 hours post drug administration.

Assay

Indomethacin in urine was determined adopting Ghorab et al.[6] modification of Hucker et al.[4] method.

Pharmacokinetics

Cumulative amount excreted, percent dose excreted, peak excretion rate (Q_{max}) and peak excretion time (t_{max}) were taken from actual measured concentrations. The elimination rate constant (K_{el}) and the elimination half life ($t_{\frac{1}{2}el}$) were calculated by linear regression analysis of the terminal linear phase of log amount remaining to be excreted versus time curves and first order equation, respectively.

Statistical Evaluation

Analysis of the results for significance was by the t test (P 0.05).

RESULTS AND DISCUSSION

The biological availability of a drug from a preparation has been used to describe a number of concepts including the extent of absorption of the drug into the blood stream, the availability of the drug at receptor sites, and the therapeutic effectiveness of the preparation[7]. In this study, the cumulative amounts and the percent dose of indomethacin excreted, following the administration of the investigated treatments, were statistically non-significant (P> 0.05) and can be arranged in descending order as follows: Treatments No. 1, 5, 3, 2 and 4 (Table 1).

The peak serum concentration, C_{max}, was suggested to be a function of both rate and extent of drug absorption, while the time necessary to reach that peak is only a function of the rate of drug absorption[8]. Similarly, the peak height of urinary excretion rate curve, Q_{max}, and the time necessary to reach that peak, t_{max}, can be considered as suitable parameters to describe the rate and extent of indomethacin absorption. Q_{max} of the investigated treatments was found to be statistically non-significant (P>0.05) and can be arranged, in descending order, as follows: Treatments No. 5, 2, 3, 1 and 4. On the other hand, t_{max} was found to be 0.5 hour for Treatments No. 1 and 5, while it was 1.5 hours for the other treatments (Table 1 and Figure 1).

Table 1 obviates that K_{el} and $t_{\frac{1}{2}el}$ of Treatments No. 2 and 5 were statistically significant (P<0.05), while those of the other treatments were non-significant (P>0.05) and can be arranged, in descending and ascend-

TABLE 1

Pharmacokinetic Parameters of Different Indomethacin Treatments

Parameter \ Treatment	Standard 50 mg Indomethacin Capsule (1)	"Indocid" Capsules (2 x 25 mg) (2)	Indomethacin Tablets (2 x 25 mg) (3)	Indomethacin Sodium Tablets (2xeq.of 25) (4)	Indomethacin Meglumine Tablets (2xeq.of 25) (5)
Cumulative amount excreted, mg	14.69±0.94*	13.44±0.49 ¢	13.55±0.56 ¢	12.40±0.27 ¢	13.86±0.31 ¢
Percent dose excreted	29.38±1.88	26.88±0.99 ¢	27.10±1.11 ¢	24.80±0.54 ¢	27.72±0.64 ¢
Peak excretion rate, Q_{max}, mg/hr.	2.95±0.32	3.05±0.30 ¢	3.04±0.37 ¢	2.88±0.21 ¢	3.66±0.15 ¢
Peak excretion time, t_{max}, hr.	0.5	1.5	1.5	1.5	0.5
Elimination rate constant, K_{el}, $hr.^{-1}$	0.119±0.013	0.168±0.022 @	0.138±0.019 ¢	0.123±0.017 ¢	0.172±0.018 @
Elimination half life, $t_{\frac{1}{2}el}$, hr.	5.79±0.53	4.11±0.57 @	5.00±0.50 ¢	5.61±0.44 ¢	4.01±0.45 @
Relative** bioavailability %		91.49±7.52	92.24±8.40	84.41±5.12	94.35±5.74

* ± S.E. @Statistically Significant ($P<0.05$) ¢Non-Significant ($P>0.05$)

** Relative Bioavailability % = $\frac{\text{Urine Indomethacin (0-24) Following Administration of (2-5)}}{\text{Urine Indomethacin (0-24) Following Administration of (1)}} \times 100$

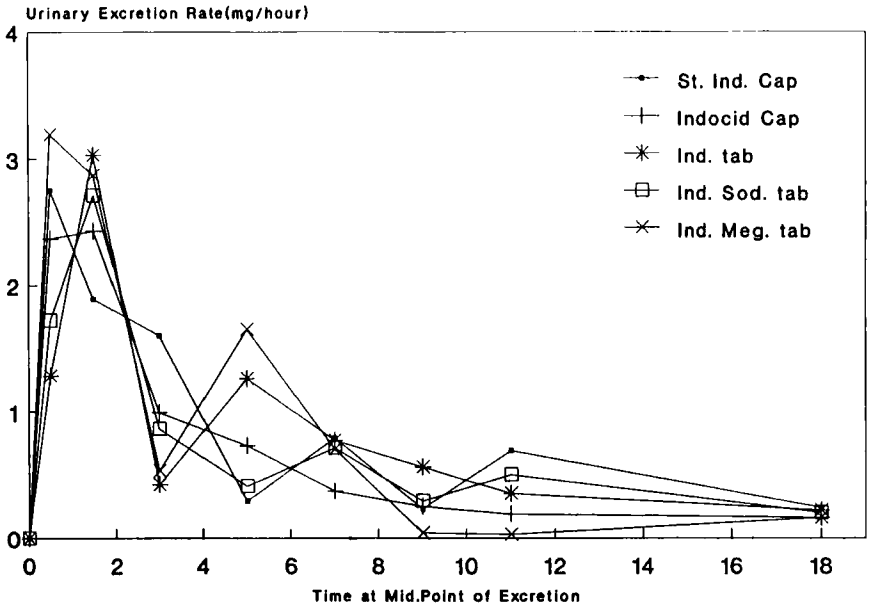

Fig.(1): Mean Urinary Excretion Rates of Indomethacin Following Oral Administration of different Treatments to Six Subjects.

ing orders, respectively, as follows: Treatments No. 5, 2, 3, 4 and 1.

From Table 1, the percentage relative bioavailability of the tested treatments can be arranged, in descending order, as follows: Treatments No. 5, 3, 2 and 4.

It is worth to conclude that directly-compressed film-coated indomethacin meglumine tablets, which was found to be the most stable and to have the best in-vitro dissolution rates[5], had the highest Q_{max} and K_{el}, the shortest t_{max} and $t_{\frac{1}{2}el}$ and the best relative bioavailability.

REFERENCES

1. K. Brune, Eur. J. Rheumatol. Inflamm., 9, 18 (1987).

2. A. Osol, R. Prott, and D.M. Altschul, "The United

States Dispensatory and Physicians Pharmacology", 26th Ed., J.B. Lippincott Co., Philadelphia, 1967.

3. R.E. Harman, M.A.P. Meisinger, G.E. Davis, and F.A. Kuebl, J. Pharmacol. Exp. Ther., 143, 215 (1964).
4. H.B. Hucker, A.G. Zacchei, S.V. Cox, D.A. Brodie, and N.H.R. Cantwell, J. Pharmacol. Exp. Ther., 153, 237 (1966).
5. A.B. Yassin, Ph.D. Thesis, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt, 1990.
6. M.M. Ghorab, F.F. Mansour, and N.N. Afifi, Egypt. J. Pharm. Sci., 28, 353 (1987).
7. "The Pharmaceutical Codex", 11th Ed., The Pharmaceutical Press, London, 1979.
8. W.A. Ritschel, "Handbook of Basic Pharmacokinetics", Drug Intelligence Publications Inc., Hamilton, 1971.