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Note

Study of the bioavailability of four indomethacin suppository formulations in healthy volunteers

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Abstract

The bioavailability of four different 100 mg indomethacin suppository formulations was determined in healthy male volunteers. Two marketed formulations, Indocid® and Dolcidium®, and a triglyceride (Witepsol H 15) supplemented with 5% monoglycerides (Dim. LS) or 9% fatty acids and 1% fatty acid methyl esters (FA/FAME) were included in the study. The $AUC_{0-12\,h}$ ($\mu g\ h\ ml^{-1}$) was (mean ± S.D.) 9.51 ± 4.06, 8.96 ± 2.55, 10.78 ± 5.64 and 11.01 ± 5.07 for the Indocid®, Dolcidium®, Dim. LS and FA/FAME formulations, respectively. The bioavailability parameters for the marketed formulations were comparable to those reported for similar formulations in the literature. The values of the two supplemented triglyceride formulations were not significantly different from those obtained from the reference formulation, Indocid®. As the addition of monoglycerides and fatty acid-fatty acid methyl esters to a triglyceride suppository base not only enhances rectal absorption but also reduces rectal mucosal irritation in rabbits, these additives might be useful for rectal drug administration. However, further experiments with larger groups of volunteers or patients, using multiple applications, are necessary in order to reveal the suitability and safety of these excipients as alternatives for those presently used in suppository formulations.

Key words: Suppository; Monoglyceride; Fatty acid; Absorption enhancer; Indomethacin; Side effects; Bioavailability; Human

Triglycerides are often used as excipients for the production of suppositories. As well as polyethylene glycol, they have been shown to induce rectal irritation in rabbits when used repetitively (De Muynck et al., 1991). The degree of rectal irritation was reduced by coadministration of monoglycerides or a blend of fatty acids and fatty acid methyl esters with the triglyceride.

In view of the species dependency of bioavailability results for indomethacin found previously in animal studies (De Muynck et al., 1994), the bioavailability of four 100 mg indomethacin suppositories was studied in two parallel cross-over studies, in healthy volunteers. In each study, two suppository formulations were administered in a single dose with a 1 week time interval. The bioavailability of Indocid® (Merck, Sharp and Dohme, Brussels, Belgium) and Dolcidium® (Galephar, Brussels, Belgium) was determined in the first study as no data are available for these

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marketed formulations containing 100 mg indomethacin. In the second study, bioavailability data were obtained for a triglyceride formulation (Witepsol H 15; Hüls AG, Witten, Germany) to which 5% monoglyceride (Dimodan LS; Grindsted N.V., Antwerpen, Belgium) (henceforth referred to as Dim. LS) or a mixture of 9% fatty acid-1% fatty acid methyl esters (Vandemoortele, Izegem, Belgium) (designated as FA/FAME) were added. These results were related to the reference formulation (Indocid®).

For the suppositories containing indomethacin in suspension, micronized indomethacin (particle size < 10 μm, European Pharmacopoeial grade, Esteve Quimica, Barcelona, Spain) was used.

In both studies six healthy male volunteers (23–40 years, 62–83 kg for the first study; 23–30 years, 62–76 kg for the second study) were included. Within 2 weeks before the beginning of the study, the volunteers had a complete medical examination including electrocardiography. The participants gave written informed consent after receiving information about the study setup and about possible side-effects of indomethacin or the suppository base. The study was approved by the medical ethics committee of the Medical School in Gent.

From 8 p.m. on the evening before the experiment the volunteers fasted and were not allowed to smoke or to consume alcoholic beverages. The intake of alcohol and smoking were also forbidden during the study days.

A suppository was administered at 8 a.m. and blood samples (5 ml) were obtained at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10 and 12 h after suppository administration. Plasma was separated by centrifugation (6 min at 3000 rpm) and frozen (−20°C) until analysis.

During the first 2 h after administration, the volunteers remained in the semi-supine position. A standard lunch was provided at 4 h after drug intake; supper could be composed as desired. Water intake was allowed over the whole study day.

Plasma samples were analysed by RP-HPLC using a validated method described elsewhere (De Muynck and Remon, 1994).

The maximal plasma indomethacin concentration (C_{max}) and the time to reach the maximal plasma concentration (t_{max}) were determined from the individual plasma concentration-time profiles. The area under the curve was calculated by the log-trapezoidal rule using the ABSPLOTS program (Shumaker et al., 1988) between 0 and 12 h ($AUC_{0-12\,h}$). Results are given as means ± standard deviation. Statistical evaluation was performed on C_{max}, t_{max} and $AUC_{0-12\,h}$ using non-parametrical statistics. The Wilcoxon signed-rank test was used for comparison of the pharmacokinetic parameters obtained for two formulations, administered in the same volunteers during either the first or the second study. For inter-study comparison, the Mann-Whitney U-test was used. A p value of < 0.05 was considered to be statistically significant.

The mean plasma concentration-time profiles are shown in Fig. 1 and the pharmacokinetic parameters are given in Table 1. For Dolcidium® the mean values were calculated on five volunteers since one plasma concentration-time profile showed a constantly increasing but low absorption resulting in a C_{max} of 1.89 μg ml^{-1} after 12 h

Table 1
Mean pharmacokinetic parameters for the different formulations tested (mean ± standard deviation and ranges; n = 6)

	C_{max} (μg ml^{-1})	t_{max} (h)	$AUC_{0-12\,h}$ (μg h ml^{-1})
Indocid®	3.08 ± 0.96 (2.18–4.35)	1.60 ± 0.82 (1–2.5)	9.51 ± 4.06 (4.98–14.18)
Dolcidium® [a]	2.73 ± 0.66 (2.10–3.65)	1.00 ± 0.00 –	8.96 ± 2.55 (6.33–11.82)
Dim. LS	3.77 ± 1.16 (2.3–5.37)	1.08 ± 0.20 (1–1.5)	10.78 ± 5.64 (5.06–19.93)
FA/FAME	3.11 ± 1.00 (2.36–5.01)	1.17 ± 0.52 (0.5–2)	11.01 ± 5.07 (6.58–17.26)

No significant differences were observed between Indocid® and Dolcidium® or Dim. LS and FA/FAME for any of the pharmacokinetic parameters.
[a] $n = 5$.

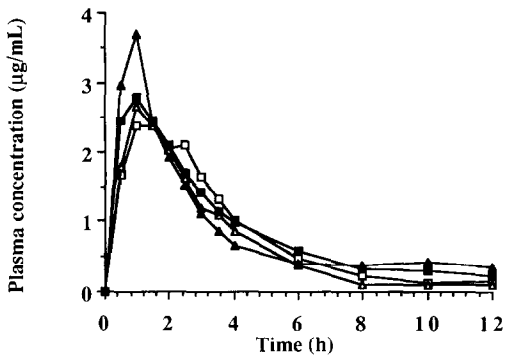

Fig. 1. Mean plasma concentration-time profiles for Indocid® (□), Dolcidium® (△), Dim. LS (▲) FA/FAME (■) after administration of 100 mg indomethacin suppositories to healthy volunteers ($n = 6$ except for Dolcidium® where $n = 5$).

and an $AUC_{0-12\,h}$ of 11.23 μg h ml^{-1}. This result is even more surprising since administration of Dolcidium® to this volunteer was followed by three smooth defecations during the morning. Reassay of all plasma samples excluded the chemical analysis as being the reason for the inconsistency with the other data.

No significant differences were observed between Indocid® and Dolcidium® or between Dim. LS and FA/FAME for any of the pharmacokinetic parameters. Absorption of indomethacin from the Indocid® formulation (t_{max} 1.60 ± 0.82 h) was somewhat slower with greater variations in comparison to the three other formulations (1.00–1.17 h). However, statistical analysis did not reveal any significant difference. The excipient for this dosage form is polyethylene glycol from which indomethacin is known to be well absorbed from the rectum. Möller (1984) reported a high bioavailability of the drug from polyethylene glycol that was not significantly different from that for a rectal aqueous suspension but significantly greater than for most fatty suppositories. Bioequivalence of two marketed 100 mg indomethacin polyethylene glycol suppositories was demonstrated by McElnay et al. (1986).

Jonkman et al. (1984) reported on the bioequivalence of a polyethylene glycol suppository and Dolcidium® 50 mg indomethacin suppositories. In a study by Aiache et al. (1987), bioequivalence between polyethylene glycol and Suppocire AP (the excipient used in Dolcidium® suppositories) suppositories containing 100 mg indomethacin was shown. However, the particle size of the suspended indomethacin was not mentioned.

No significant difference was found in C_{max}, t_{max} and $AUC_{0-12\,h}$ values between Indocid® and Dolcidium®, confirming the results obtained for similar formulations by Jonkman et al. (1984) and Aiache et al. (1987). Bioavailability experiments in rabbits have shown similar C_{max} values after Indocid® and Dolcidium® administration in contrast to data from analogous experiments in dogs, where significantly higher C_{max} and AUC values were observed for Indocid® (De Muynck et al., 1994).

For both Witepsol H 15 supplemented formulations the values for C_{max} and $AUC_{0-12\,h}$ were apparently higher than for both marketed formulations. However, these differences were not significant.

Adding monoglycerides to the triglycerides apparently enhanced the bioavailability, confirming the results we obtained in dogs (C_{max} and AUC) and rabbits (C_{max}) (De Muynck et al., 1994). Linoleic acid based monoglycerides, such as Dimodan LS, have been shown to be absorbed from the rectum (Christophe et al., 1987). In the epithelial cell, these *cis*-unsaturated fatty acid monoglycerides disorder the hydrophobic region of the membrane's interior and interact with the polar head groups of phospholipids inducing an increase in permeability of these cells (Muranishi, 1990). Monoglycerides can also solubilize cholesterol, a membrane stabilizer, which could result in facilitated transcellular transport (Van Hoogdalem, 1988).

It is unlikely that the high availability of the fatty acid-fatty acid methyl ester supplemented formulations can be attributed to methyl esters of long chain fatty acids, since they have been shown not to increase the permeability of liposomal membranes (Muranishi et al., 1981). The pH in the rectum of normal subjects was found to be 7.9 (Bitterman et al., 1967). At this pH the long chain fatty acids become partially ionized and their affinity for monolayers of the epithelial cell wall is comparable to that of membrane phospholipids

Table 2
Side-effects after administration of the different suppository formulations (n = 6)

	Indocid®	Dolcidium®	Dim. LS	FA/FAME
Abdominal spasms	–	–	2	2
Tenesmus	1	–	–	1
Flatulence	–	–	–	1
Diarrhoea	1	1	2	2
Flush	1	1	–	–
Dizziness	1	–	–	1

(Scow and Blanchette-Mackie, 1985). In the membrane *cis*-unsaturated long chain fatty acids increase both transcellular and paracellular permeability by changing the lipid bilayer permeability and influence protein-lipid interactions (Muranishi, 1990). In rats, the absorption enhancing effect of long chain fatty acids on the rectal absorption of indomethacin was reported using oleic acid in a hydrogel (Kamiya et al., 1983).

This enhanced bioavailability of indomethacin from the fatty acid-fatty acid methyl ester supplemented formulation confirms the findings with dogs where an even greater availability than with monoglyceride supplemented formulations was observed. This enhancement in bioavailability (C_{max}) was not confirmed in rabbits (De Muynck et al., 1994).

The side-effects are tabulated in Table 2. Diarrhoea was the complaint most often reported and was observed with all four suppositories. Abdominal spasms only occurred after the administration of Witepsol supplemented suppositories. Tenesmus, flatulence, flush and dizziness were reported once for some of the suppository formulations. No nausea or vomiting was reported. The side-effects observed in this study have also been reported in the literature as being induced by the drug rather than by the formulation (Woolf, 1965; Huskisson et al., 1970; Alvan et al., 1975; Baber et al., 1980; Jonkman et al., 1984; Möller-Jensen and Grenabo, 1985).

1. References

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