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Rectal versus oral absorption of diflunisal in man

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Summary

Rectal absorption of diflunisal from various dosage forms was studied in man. The rectal dosage forms included fatty and macrogol suppositories, an aqueous suspension and solutions with various solvents in order to achieve complete dissolution of diflunisal. A comparison was made with an orally administered suspension. The plasma concentrations of diflunisal were measured by means of HPLC analysis after a single dose of 250 mg diflunisal in a cross-over study in 7 volunteers.

Compared with oral administration, rectal absorption conditions are limited as a consequence of the poor solubility characteristics of diflunisal. Therefore attempts were made to improve absorption conditions by varying the nature of the rectal dosage form. The addition of alkali and solvents such as polyethylene glycol and glycofurol, did result in an increase of the rate of absorption, whereas the bioavailability 8 h after administration did rise up to 80% as compared with oral dosing. In the case where suppositories are employed, a fatty vehicle rather than a water-soluble base should be chosen in order to stimulate the driving force for absorption. It is concluded that 500 mg diflunisal suspended in a 4 ml fatty mass results in peak plasma concentrations comparable with an oral dose of 250 mg diflunisal.

Introduction

Diflunisal, a salicyclic acid derivative, is an effective anti-inflammatory analgesic. It has a relatively long plasma half-life (± 11 h) which permits a reduction of dosing frequency to twice daily dosage. In addition less side-effects compared with the

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salicylates at equipotent doses has been reported (Brogden et al., 1981). For this reason, especially its use in the treatment of rheumatic diseases can be seriously considered (Dundee and McCaughey, 1980).

There appears to be increasing interest in rectal administration of anti-inflammatory analgesics (De Boer et al., 1982). Acetylsalicylic acid, propionic acid and phenylacetic acid derivatives are well absorbed rectally and it is remarkable therefore that no studies have been performed so far concerning rate and extent of rectal absorption of diflunisal. We therefore designed a cross-over study in healthy volunteers to investigate the nature of the rectal absorption process of diflunisal, by measuring plasma concentrations of diflunisal by means of HPLC analysis after administration of micro-enemas and suppositories. To establish differences in rate and extent of absorption a comparison was made with an orally administered aqueous suspension of diflunisal.

Materials and Methods

Dosage forms

The oral dosage form consisted of 250 mg diflunisal which was obtained from MSD (Haarlem, The Netherlands), suspended in 50 ml water. For rectal use aqueous suspensions were prepared containing 250 mg diflunisal suspended in 10 ml of a medium which consisted of 1.0% methylcellulose 400 cps in distilled water. The pH was adjusted to, respectively, 4.5 and 7.0 with 0.01 M sodium hydroxide. Rectal solutions were prepared containing 250 mg diflunisal dissolved in 10 ml of a mixture of glycofurol (Merck) and water (1 : 1) or a mixture of polyethylene glycol 400 and water (1 : 1). The pH was adjusted to 7.0.

Suppositories were prepared by mixing diflunisal with a molten base of Witepsol H15 (Interpharm) or a mixture of PEG 1540/PEG 4000 (1 : 2), poured into brass moulds (3 and 4 ml) and stored in the refrigerator for one night before use. The suppositories contained 250 mg and 500 mg diflunisal (272.5 mg sodium diflunisal) which was obtained from MSD (Haarlem, The Netherlands).

Experiments in volunteers

Seven healthy human subjects, female and male, ranging in age from 20 to 25 years and in body weight from 53 to 81 kg, participated in the cross-over study. No drugs were taken for two weeks prior to and during the study. The experiments were initiated at 09.00 h and the volunteers did not take any food during the morning. They were asked to remain in a sitting position. No discomfort following application of any rectal dosage form was reported by the volunteers. Blood samples of 10 ml were taken using Venoject tubes (Terumo Corporation) containing 15 mg sodium EDTA granules at 0, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0 and 8.0 h after administration. Plasma obtained by centrifugation was immediately frozen until analyzed.

Determination of diflunisal in plasma

Chromatographic conditions. A liquid chromatograph (Waters Ass.) equipped

with an UV-detector (Model 440) set at 254 nm was employed. The detector was operated at 0.02 AUFS. The column (25 cm × 4.6 mm) was packed with Lichrosorb 10 RP 18 and guarded with a pre-column Vydac 201 SC (10 cm × 2.1 mm). Both columns were made by Chrompack N[illegible] 'erland. The mobile phase was 40% (v/v) 0.007 M phosphate buffer solution (pH 7.2) in methanol. The flow rate was 2.0 $ml \cdot min^{-1}$.

Procedure in plasma. To 1.0 ml plasma 3.0 ml of the internal standard solution (150 µl of nitrobenzene (Merck, Darmstadt, F.R.G.) in 1000 ml of methanol) was added. After shaking for 10 min the content of the tube was centrifuged during 5 min at 3000 *g*. 100 µl of the liquid was injected into the HPLC. The retention times were respectively: diflunisal 2.7 min and nitrobenzene 4.0 min.

With 1.0 ml plasma samples this method is accurate to concentrations as low as 1.0 µg/ml plasma.

Results and Discussion

Aqueous dosage forms

The data in Table 1 and Fig. 1 show that diflunisal was readily absorbed from the orally administered suspension: the mean (n = 7) peak plasma concentration being 40.7 $\mu g \cdot ml^{-1}$ was reached within 2 h. The mean plasma elimination half-life was estimated to be 9.2 ± 0.7 h. These results are in good agreement with the kinetic data of Steelman et al. (1975) following plasma concentration–time profiles for diflunisal after oral administration of 250 mg diflunisal.

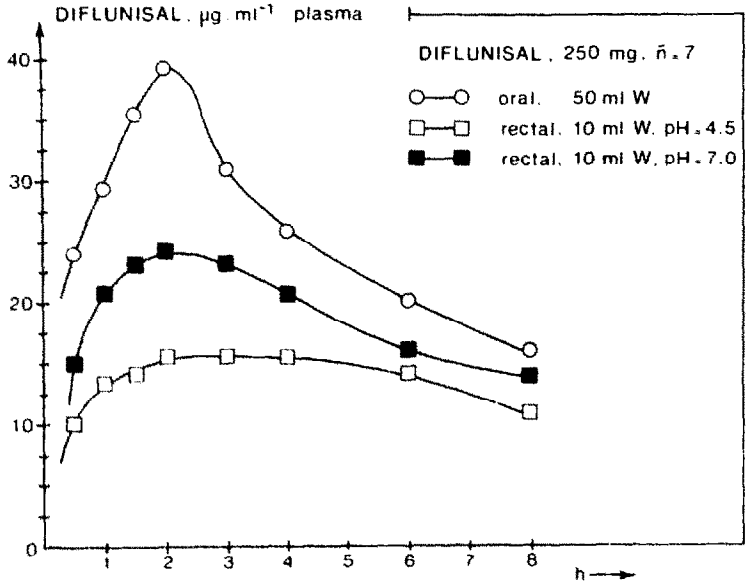

Fig. 1. Plasma concentration–time profiles of diflunisal after oral and rectal administration of aqueous dosage forms containing 250 mg of diflunisal. The data represent mean values out of 7 volunteers for each dosage form. Standard deviations are indicated in Table 1.

TABLE 1

ABSORPTION CHARACTERISTICS OF DIFLUNISAL (mean ± S.D.) FROM DOSAGE FORMS AFTER RECTAL AND ORAL ADMINISTRATION OF DIFLUNISAL (250 mg) TO 7 HEALTHY VOLUNTEERS

Plasma conc. diflunisal ($\mu g \cdot ml^{-1}$) at t =	Oral susp., 50 ml	Rectal susp., 10 ml		Rectal sol., 10 ml		Rectal suppos., 3 ml	
		pH = 4.5	pH = 7.0	Glyc/W	PEG_{400}/W	Fatty base	PEG base
0.5 h	24.0 ± 10.8	10.5 ± 0.8	15.2 ± 2.0	11.8 ± 5.1	10.2 ± 5.9	9.2 ± 1.9	3.2 ± 1.8
1.0 h	28.9 ± 8.3	12.9 ± 0.8	21.2 ± 2.5	20.0 ± 4.5	18.5 ± 9.8	15.6 ± 4.5	8.0 ± 3.2
1.5 h	36.7 ± 7.6	14.4 ± 0.6	23.4 ± 1.6	24.6 ± 5.2	21.1 ± 9.6	19.9 ± 6.3	12.6 ± 2.8
2.0 h	38.6 ± 4.0	15.6 ± 1.4	24.4 ± 2.3	27.0 ± 5.3	21.6 ± 8.4	20.8 ± 6.0	17.1 ± 3.6
3.0 h	31.0 ± 3.9	16.5 ± 1.9	22.6 ± 4.1	28.0 ± 7.1	20.1 ± 7.4	21.2 ± 6.7	19.3 ± 2.4
4.0 h	26.0 ± 2.8	16.3 ± 2.5	20.9 ± 4.6	25.5 ± 7.0	18.2 ± 5.4	19.9 ± 6.5	19.4 ± 3.3
6.0 h	20.0 ± 2.2	13.9 ± 3.7	15.9 ± 3.7	19.2 ± 4.7	15.8 ± 6.0	15.2 ± 4.9	13.6 ± 2.4
8.0 h	16.2 ± 2.1	11.2 ± 2.8	13.6 ± 3.9	15.7 ± 4.2	14.1 ± 5.3	12.7 ± 4.3	10.9 ± 2.1
number	7	5	5	7	7	7	7
C_{max} ($\mu g \cdot ml^{-1}$)	40.7 ± 4.1	17.1 ± 2.0	24.5 ± 2.3	28.5 ± 6.7	22.5 ± 7.9	22.4 ± 6.5	21.1 ± 2.9
t_{max} (h)	1.7 ± 0.3	3.0 ± 1.0	2.2 ± 0.6	2.2 ± 0.8	3.0 ± 2.6	2.6 ± 1.1	3.0 ± 0.8
AUC_{0-8h} ($\mu g \cdot ml^{-1} \cdot h$)	199.9 ± 27.3	110.7 ± 15.0	147.5 ± 26.3	168.8 ± 35.8	134.3 ± 44.6	132.1 ± 36.2	111.1 ± 12.6
F_{rel} (%)	100	55	74	84	67	66	56

After rectal administration of the weakly acid aqueous suspension of diflunisal a substantial difference in rate and extent of absorption compared with the oral dose occurred: the mean C_{max} of 17.1 $\mu g \cdot ml^{-1}$ was reached at 3.0 h after dosing and the bioavailability 8 h after administration was found to be only 55% as compared with oral dosing.

The absorption profiles after oral and rectal administration differed significantly ($P < 0.05$). Obviously rectal absorption conditions are less favourable probably due to the poor solubility characteristics of diflunisal. This dissolution rate-limited absorption profile could be demonstrated by adjusting the pH of the micro-enema to 7.0. Although the proportion of the undissociated form of diflunisal now decreases (pK_a is 3.3) the solubility of the drug is markedly increased. From Table 1 and Fig. 1 it can be concluded that the net result is a more rapidly absorption: the C_{max} of 24 $\mu g \cdot ml^{-1}$ is reached now within 2.5 h, whereas the bioavailability 8 h after administration is about 75% compared with oral dosing. These differences were found to be significant ($P < 0.05$) compared with the weakly acid micro-enema.

In order to enhance the driving force for rectal absorption further, it is possible to add solvents which can improve the solubility of slightly soluble drugs (Moolenaar et al., 1981). Therefore a rectal solution of 250 mg diflunisal in 10 ml solvent was prepared, using a mixture of glycofurol and water (1 : 1). The pH was adjusted to 7.0. Table 1 and Fig. 2 demonstrate, however, that the absorption profile of diflunisal after dosing with the glycofurol solution coincides fairly well with the rectal aqueous suspension (pH 7.0), indicating that the driving force for absorption is not improved. Similar results were obtained after dosing with a 50% polyethylene

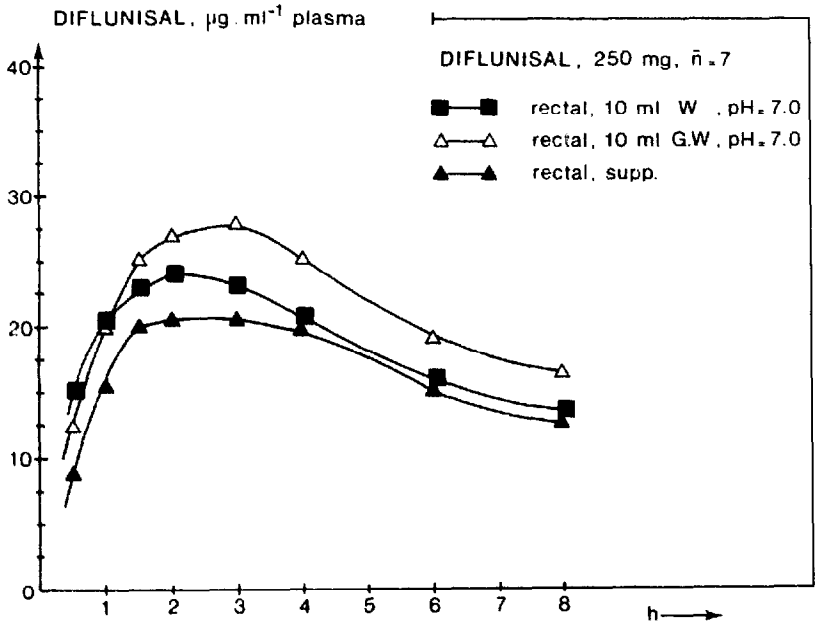

Fig. 2. Plasma concentration–time profiles of diflunisal after rectal administration of various dosage forms containing 250 mg of diflunisal. The data represent mean values out of 7 volunteers for each dosage form. Standard deviations are indicated in Table 1.

glycol 400 solution, as shown in Table 1. Thus, more complete dissolution using certain solvents does not necessarily result in a positive effect on the driving force for absorption. In this respect it could be clearly demonstrated that the addition of solvents such as polyethylene glycols, does influence the polarity of the vehicle, probably resulting in a decrease in the partition of the drug under study between solvent and rectal lipoid (Vromans and Moolenaar, 1984). In agreement with quantitative absorption studies of Kakemi et al. (1965), such a decrease in partition may result in a reduction of the driving force for absorption.

Yet, in view of the AUCs for the rectal solutions, it can be concluded that the extent of absorption 8 h after administration was rather complete (84% compared with oral dosing).

Suppositories

As a result of the poor dissolution characteristics of diflunisal, absorption from a fatty suppository resulted in a sustained absorption profile (Fig. 2): the mean C_{max} of 22.4 $\mu g \cdot ml^{-1}$ was reached at 2.6 h after dosing, whereas the bioavailability 8 h after administration was found to be approximately 65% compared with oral dosing (Table 1).

In the case of a fatty suppository vehicle, Schoonen et al. (1979) concluded that as far as slowly dissolving drugs are concerned, increasing the drug concentration in the vehicle or enlarging the volume of the vehicle chosen may influence the rectal absorption rate in a different way. For diflunisal these two effects are demonstrated in Fig. 3. When 500 mg instead of a 250 mg dose of diflunisal is rectally applied, no substantial difference in absorption rate occurs: the higher dose administered in the same suppository volume resulted only in a prolonged absorption process. On the

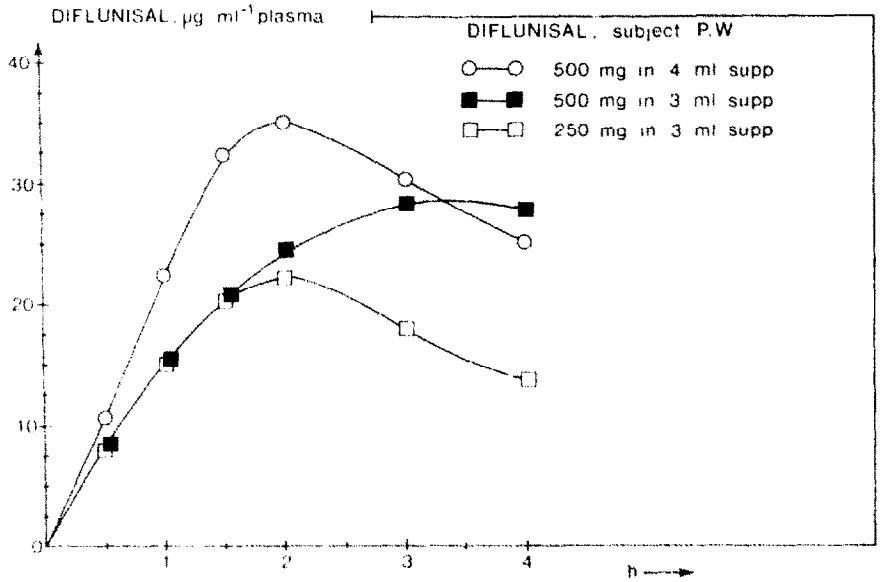

Fig. 3. Plasma concentration–time profiles of diflunisal after rectal administration of different doses, suspended in different volumes of fatty suppository mass, to one volunteer.

other hand, an increased volume of the suppository mass (4 ml), resulting in a larger absorption surface area in the rectum, leads to a higher uptake rate of the suspended drug (Fig. 3).

Two other factors may influence the release of diflunisal from a suppository dosage form: the use of the sodium salt instead of the free acid or the choice of a water-soluble suppository vehicle instead of a fatty one. In vitro measurements obtained with the sodium salt indicated that the release rate from a fatty suppository was only slightly increased, probably due to unusually low water solubility for a sodium salt (1 in 60). The effect of using a water-soluble suppository vehicle (PEG 1540/4000, 1:2) on the rectal absorption rate is shown in Table 1. The use of water-soluble bases clearly delayed the rate of diflunisal absorption. Since polyethylene glycol suppositories in general are quickly dissolved in the rectal secretory fluid it is likely that the reduced absorption rate observed is due to a less favourable partition between vehicle and rectal lipoid as discussed above.

It can be concluded that rectal dosing of diflunisal is feasible but that absorption is slow and incomplete due to dissolution rate limitation. Relative bioavailability and absorption rate, however, can be improved considerably if diflunisal is dissolved in micro-enemas containing solvents such as glycofurol. In the case of suppositories, a fatty vehicle should be chosen using 500 mg of diflunisal suspended in a 4 ml mass. With this dosage form it is possible to obtain peak plasma concentrations comparable with those following an oral dose of 250 mg diflunisal.

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