DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 13(2), 213-224 (1987)

A COMPARISON OF THE BIOAVAILABILITY OF PARACETAMOL FROM A FATTY AND A HYDROUS SUPPOSITORY BASE AND THE EFFECT OF STORAGE ON THE ABSORPTION IN MAN

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ABSTRACT

Rectal absorption of paracetamol from a fatty and a hydrous base was studied in ten healthy volunteers after administration of freshly prepared suppositories and suppositories stored for four years. Aging markedly affected the absorption from fatty suppositories decreasing the extent of paracetamol bioavailability. Some physical measurements were conducted in order to obtain information about the nature of the changes which occured during storage.

Rectal suppositories are solid dosage forms adapted for introduction in the rectum. They usually either melt at body temperature or dissolve in anorectal fluids. When a systemic therapeutic effect is desired the active ingredient must be released from the dosage form and absorb.

Evaluation of the bioavailability of the active ingredient in new formulations for suppositories is usually performed by comparing a relatively freshly prepared product with an already marketed generic product, either a suppository or an oral dosage form. However, as in any rational dosage form design, the stability of the final product is critical. It is possible that storage could influence - among other

factors - the physical properties of the product. Any such changes could result in altered bioavailability.

The effect of storage on different characteristics of suppositories is well established (1). It has been suggested many times that such changes may result in decreased bioavailability. However, only a few papers describing studies in humans in which such changes in bioavailability were observed have been published. Studies in healthy volunteers were therefore planned in order to investigate possible differences in the rate and extent of absorption of paracetamol between freshly prepared water soluble and fatty suppositories and the corresponding four years old products. Some observations on the physical properties of the fatty base were also made.

EXPERIMENTAL

Preparation of the suppositories

Suppositories containing 100 mg of paracetamol (micronized, Ph. Eur.) were prepared with two different bases:

A. A fatty base (Novata E, Degussa, Frankfurt) consisting of a mixture of mono-, di- and triglycerides of natural saturated fatty acids with chain lengths of C12 - C18 and 0.8 per cent of polysorbate 80 and

B. A water soluble base consisting of a mixture of carbowaxes 4000 (B.P.) and 6000 (Ph.Nord.) and glycerol (Ph.Eur.) in a ratio of 8:1:1.

The bases were melted in a water bath at 50°C and paracetamol added to form a suspension. The masses were cooled to 36 - 38°C with gently stirring, poured into molds and allowed to solidify at room temperature.

Absorption studies

Absorption studies were performed using suppositories which had been stored for four years at room temperature and freshly prepared suppositories. Paracetamol as an oral solution (Polarfen 25 mg/ml, Medipolar, Oulu, Finland) served as the reference formulation.

The studies were carried out in 10 healthy ambulatory volunteers, 9 females and one male. The subjects were shown by medical examination, blood chemistry and haematology to be in good physical condition. They gave their consent after the objectives and the procedures of the trial had been explaned to them. No other drugs and alcohol were per-

mitted one week before and during the study. It was accomplished following a randomized cross-over design with one week's wash-out period between the experiments.

The subjects received 100 mg doses of paracetamol at 8 o' clock a.m. after an overnight fast. Before administration of the suppository they were asked to empty their bowels and not to defecate for at least 5 hours after dosing. Eating was not allowed untill 4 h post-administration.

Paracetamol levels in serum were followed by taking blood samples before administration and at 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, and 8 hours after dosing. Serum was separated by centrifugation and stored frozen (-20°C) until analyzed.

Determination of paracetamol in serum

Serum paracetamol concentrations were determined by a method based on quantitative thin layer chromatography as follows.

One ml of serum was taken into a test tube followed by addition of 5 ml of diethylether and N-butyl-p-aminophenol (1 µg) as internal standard. After shaking for 15 minutes the content of the tube was centrifuged. 4 ml of the organic phase was transferred to another tube and the solvent evaporated. The residue was dissolved into 45 µl of ethylacetate. Using an automated line-applicator (Linomat III, Camag) 30 µl of this solution was applicated to a TLC plate (Silica gel 60, Merck). Chloroform-acetone (3+2) was used as mobile phase. Paracetamol and the internal standard were measured directly from the plate using a chromatogramspectrophotometer (Zeiss KM3) in the reflectance mode at 247 nm. Paracetamol concentrations were calculated from the ratios of the peak heights (paracetamol/internal standard). A series of serum samples to which various concentrations of paracetamol (0-2 µg/ml) had been added were prepared simultaneously, treated similarly and used to construct a calibration curve.

The method measures unchanged paracetamol. The lower limit of detection was about 50 µg/l and the reproductibility was 3.9 per cent and 5.7 per cent (RSD) at 1.5 and 0.3 mg/l, respectively.

Calculations

In the pharmacokinetic calculations the one compartment open model with a lag time and first order kinetics were used. Almost in all cases the data fitted the model well (Fig.1). The fitting was unsatis-

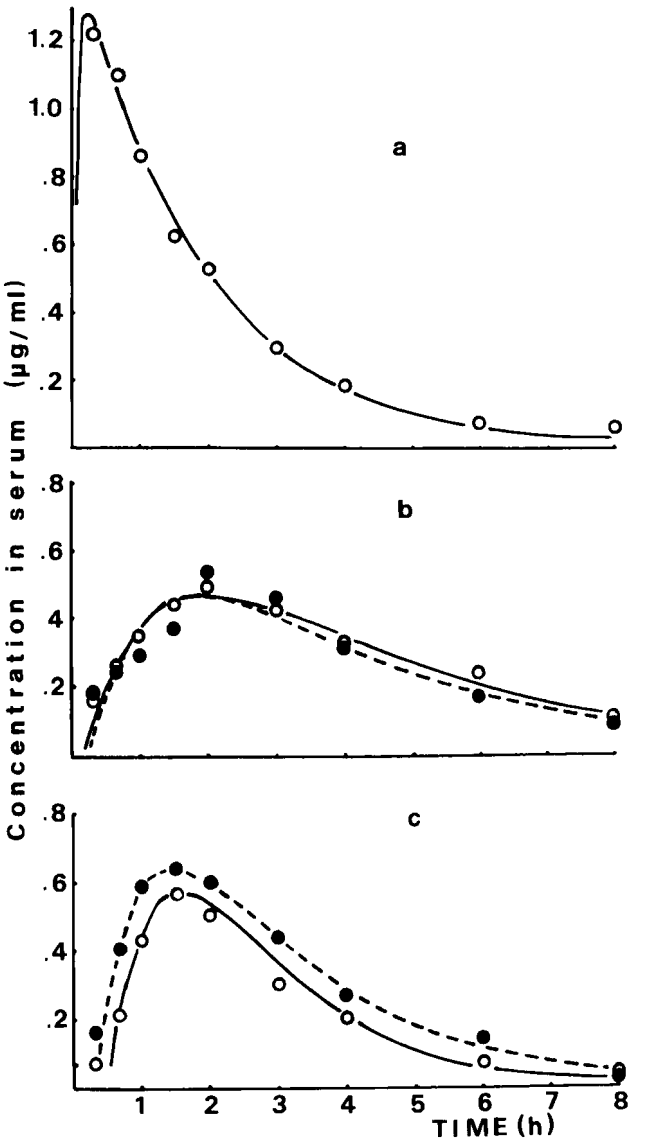

FIGURE 1.

Paracetamol Concentrations in Serum for a Volunteer (ML). Observed points and Calculated Lines. a. Oral Solution, b. Hydrous Suppositories and c.Fatty Suppositories. Solid Circles and Dotted Lines Fresh Preparations, Open Circles and Solid LinesFour Years Stored Suppositories.

factory for the curves of KU, TN, and TJ when they received stored hydrous suppositories, stored fatty suppositories, and freshly prepared fatty suppositories, respectively.

The elimination rate constant (ke) was determined by the use of the log-linear regression analysis of data in the post-absorption phase. The absorption rate constants (ka) were estimated by the Wagner-Nelson method (2). The values of peak concentrations (Cmax) and the times to concentration maxima (tmax) were calculated utilizing the formula given by Gibaldi and Perrier (3). The area-under-the-curve (AUC) was determined by the trapezoidal approximation with extrapolation to infinity.

The statistical significance of differences was determined by Student's t-test for paired data.

Physical studies

Differential scanning calorimetric and X-ray diffraction measurements were accomplished for fatty suppositories.

Differential scanning calorimetric measurement conditions were as follows: Mettler 3000 system, a heating rate of 2^{o}C/min from 25 to 45 ^{o}C.

X-ray diffraction measurement conditions were: Philips PW 1130, radiation Ni-filtered $Cu_{2\alpha}$, voltage/current ratio 44 kV/16 A, scanning speed 1^{o}C/min, divergence/receiving slits 0.5/0.3 mm.

RESULTS

Absorption studies

Mean serum levels and calculated pharmacokinetic parameters are collected in Tables 1 and 2, respectively. As expected, administration of the oral solution resulted in higher peak concentrations in a shorter time than did the rectal route of administration. This did not depend so much on the onset of absorption i.e. lag time as on the absorption rate. The absorption rate constant for the oral solution was significantly higher than for suppositories with the exception of freshly prepared fatty suppositories. In spite of the rate differences, the extent of bioavailability was not dependent on the route of administration.

TABLE 1.

Mean Serum Paracetamol Levels (mg/l) Following Administration of a Single 100 mg Dose as Different Preparations. SD in Parentheses.

Time after dosing (h)	Oral solution	Suppositories: Hydrous fresh	Suppositories: Hydrous stored	Suppositories: Fatty fresh	Suppositories: Fatty stored
0.33	1.04(0.57)	0.29(0.20)	0.24(0.32)	0.24(0.07)	0.28(0.15)
0.67	1.36(0.73)	0.74(0.28)	0.42(0.32)	0.54(0.27)	0.54(0.21)
1	1.04(0.36)	1.05(0.54)	0.71(0.38)	0.60(0.20)	0.81(0.61)
1.5	0.90(0.25)	1.13(0.59)	0.85(0.55)	0.80(0.36)	0.73(0.28)
2	0.73(0.22)	0.94(0.48)	0.85(0.43)	0.79(0.27)	0.79(0.32)
3	0.52(0.24)	0.72(0.29)	0.63(0.24)	0.72(0.27)	0.63(0.27)
4	0.40(0.25)	0.60(0.37)	0.42(0.14)	0.53(0.19)	0.45(0.24)
6	0.21(0.15)	0.27(0.16)	0.18(0.06)	0.31(0.12)	0.27(0.18)
8	0.12(0.10)	0.15(0.09)	0.11(0.06)	0.16(0.09)	0.16(0.11)

The absorption of paracetamol from freshly prepared fatty suppositories was faster than from either of the hydrous ones. This led to higher peak concentrations in a shorter time even though the lag time for the freshly prepared fatty suppositories was significantly longer than that for the stored hydrous ones. No significant differences between the fatty versus hydrous bases were observed in the total amounts absorbed.

The effect of storage on the bioavailability of paracetamol from hydrous suppositories was negigible. However, age related differences were observed in the fatty suppositories. This was seen most clearly in the higher peak concentrations and the total amounts absorbed with the freshly prepared compared to the four year old fatty suppositories. The rate of absorption was, however, unaffected. The absorption rate constants and the times to peak concentration were similar. The lag time almost doubled during the storage but the difference was not statistically significant.

TABLE 2.

Calculated Pharmacokinetic Parameters (Means) for Paracetamol after a Single 100 mg Dose as Different Preparations. SD in Parentheses.

		ka (1/h)	tmax (h)	lag t (h)	Cmax (µg/ml)	AUC (µg h/ml)	ke (1/h)
Oral solution		7.716 (6.463)	0.57 (0.44)	0.03 (0.07)	1.35 (0.49)	4.145 (1.80)	0.431 (0.131)
Fatty base	fresh	2.436 (0.999)	1.05 (0.16)	0.18 (0.17)	1.20 (0.61)	4.92 (2.27)	0.352 (0.094)
	stored	1.969 (1.035)	1.14 (0.29)	0.34 (0.22)	0.96 (0.49)	3.64 (1.27)	0.473 (0.198)
Hydrous base	fresh	1.153 (0.401)	1.61 (0.19)	0.13 (0.08)	0.80 (0.34)	4.37 (1.68)	0.312 (0.088)
	stored	1.155 (0.287)	1.49 (0.42)	0.07 (0.11)	0.82 (0.46)	4.12 (2.33)	0.350 (0.093)
Significance of differences $p<0.05$		M>FS M>HF M>HS FF>HF FF>HS	M<FS M<FS M<HF M<HS FF<HF FF<HS FS<HF FS<HS	M<FS M<HF FS>HS	M>FS M>HF M>HS FF<FS FF>HF FF>HS	FF>FS	M>HF

TABLE 3.

The Effect of Storage Time at Room Temperature on the Liquid Fraction and the Melting Point of the Fatty Suppository Base determined by DSC.

Storage time (days)	Liquid fraction at 36°C (%)	Melting point (°C)
1	89.7	33.3
15	78.8	36.0
90	57.9	36.7
430	51.5	36.6
480	48.8	36.7
1779	30.3	37.9

Physical studies

A marked decrease in the liquid fraction of the fatty suppository base occured during storage, as shown in Table 3. The melting point of the base increased during storage from 33.3 to 37.9°C.

X-ray diffraction measurements showed that the structure of the base in the fresh fatty suppository is only partially crystalline. The crystallization stage incresed during storage. The crystal structure of paracetamol in the suppositories did not change on aging.

DISCUSSION

The absorption rate of paracetamol - in itself - does not depend on whether it is administered orally or rectally (4). When suppositories are used the release of the drug has, however, to be considered. These two processes - absorption and release - have to be distinguished. The slower rectal absorption as compared with the oral dosing found in the present study can be attributed to the slower release rate of paracetamol from the suppositories. No evidence for the biphasic absorption of paracetamol from suppositories suggested by Saano et al.(5) were found.

The extent of absorption from suppositories has been questioned (6,7) and the bioavailability of paracetamol from this dosage form has been shown to be lower than that from oral formulations in some stu-

dies (8). More often, however, the bioavailability of properly formulated suppositories has been found to be comparable with oral administration of equal doses, and differences observed have been considered clinically unimportant (9-11). On the other hand, it is also not possible to avoid the first pass metabolism of paracetamol by rectal administration (4). The results of the present study are in agreement with the two last mentioned statements.

Formulation of a suppository with good bioavailability requires a suitable base which melts at temperatures well below the body temperature and spreads readily in the anorectal region or dissolves in the fluids present in the rectum. Differences in the paracetamol release rates and absorption from various suppository bases have been recorded many times (7,11-14). The reasons for the differences may lie in the different particle sizes of the drug or the volume of the vehicle (15). Particle size may even change during storage (16).

Another important factor is the solubility of the drug in the vehicle used. The importance of the vehicle dielectric properties has been studied by Pagany et al.(17) and by Stavchansky et al.(18). Polyethylene glycol bases with a low solubility for paracetamol release the drug more rapid and have a better bioavailability than bases in which the drug dissolves more completely. The release and absorption rates also tend to decrease with increasing solubility of the drug in the vehicle when fatty bases are used (19).

Differences in the solubility of paracetamol in the bases may be an explanation for the observed differences found in the present study between the freshly prepared fatty suppositories and the hydrous suppositories. Particle size effects can not be excluded because, although the suppositories were prepared using the same batch of paracetamol, owing to differences in solubility differences in the particle size may appear. However, if this were a dominating factor the absorption from hydrous base should have been faster than from fatty base. An additional factor might be faster spreading of the freshly prepared fatty suppositories in the anorectal region. This would enhance absorption considerably (20).

No alteration in the absorption profile from hydrous base after four years storage were observed in the present study. No attempts were, therefore, made to find out whether physical changes had occur-

ed. This does not exclude the possibility of aging of polyethylene glycol suppositories which may lead to decreased dissolution rates for drugs (21,22).

The aging effect in the fatty base used was marked. In this respect these suppositories were not unusual. There are many reports of changes in the melting behaviour and drug release of suppositories in vitro (23-29). Though it can be said that the in vitro results do not reflect the bioavailability, the results obtained by Eckert et al.(30) indicate that melting in vitro and in vivo correspond each other. Thus any decrease in drug release rate most probably will result in decreased rate or even decreased extent of absorption.

The influence of aging of fatty suppositories on the absorption has been studied by Moes (31) and Eckert et al.(32). According to these authors rectal suppositories containing drugs for systemic action should not be prepared from fatty bases in which important modifications in the physical properties occur on aging. The present study supports this view.

The changes which occur on aging of suppositories may be either chemical or physical in nature. The first mentioned possibility has been studied by Moes (23), Ruehlow and Neuwald (33), and Thoma et al. (34). The results are rather contradictory, which is not surprising when the many possibilities for interactions between the components in suppositories are considered. More often physical changes, especially polymorphic transitions have served as an explanation for the hardening of fatty suppository bases (25,29,35-40).

The information obtained from the X-ray diffraction measurements in the present study is a better indicator of the precipitation of different phases than polymorphic transitions. This does not mean that polymorphic changes during storage of fatty suppositories can be excluded. However, the increase in the crystalline stage of the suppositories seems to be the primary phenomenon affecting the melting behaviour and the bioavailability of suppositories made of the fatty base used in this study.

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