International Journal of Pharmaceutics, 16 (1983) 41–46
Elsevier

Bioavailability of progesterone from rectal dosage forms in rabbits

A. Buur, N.Chr. Larsen, M. Rassing * and K. Hermansen **

*Department of Pharmaceutics and ** Department of Pharmacology, Royal Danish School of Pharmacy, Universitetsparken 2, DK-2100 Copenhagen (Denmark)*

(Received November 11th, 1982)
(Accepted January 13th, 1983)

Summary

The systemic availability of progesterone in two rectal dosage forms was investigated in rabbits. The progesterone plasma concentration was determined as total radioactivity (progesterone and its metabolites) after a single dose of 5 mg/kg [^{3}H]-labelled progesterone in an adeps solidus suppository (1) and in a propylene glycol enema (2) given in a randomized cross-over fashion. The equivalent dose was given intravenously (3) to the same rabbits.

The maximum plasma concentration (C_{max}) after (1) was 0.82 ± 0.43 μg/ml and significantly lower than after (2), which was 3.81 ± 1.08 μg/ml (mean ± S.E.; $P < 0.05$). The time to reach the maximum plasma concentration (T_{max}) was for (1) 1.75 ± 0.25 h and for (2) 0.56 ± 0.32 h (mean ± S.E.; $P < 0.05$). The mean plasma concentration vs time curve after (3) indicates that a multicompartment system is involved in the disposition of progesterone. The plasma half-life ($t_{1/2}$) estimated from 0–6 h was 5.10 ± 1.12 (mean ± S.E.).

The systemic availability (F%) of (1) from 0–6 h (AUC_{0-6h}) was $14 \pm 8\%$ and significantly lower than that of (2), which was $44 \pm 10\%$ (mean ± S.E.; $P < 0.05$).

The results indicate a delayed and possibly lower absorption of progesterone from the suppositories as compared to the enema.

Introduction

The natural hormone, progesterone, is used for different indications in human therapy such as insufficient corpus luteum function and threatened abortion. Pro-

* To whom correspondence should be directed.

gesterone is mainly administered as suppositories, vagitories and intramuscularly either as an oily solution or as a suspension. It is not used orally because of a high first-pass effect due to an extensive liver metabolism (Brotherton, 1976). The rectal and vaginal doses (100–200 mg) compared to the i.m. dose (5 mg) are very high, due to a poor bioavailability of the former dosage forms. The poor bioavailability of progesterone suppositories has been demonstrated by Nillius and Johansson (1971).

In an earlier work by Rassing (1979) the absorption of progesterone from adeps solidus suppositories was compared with the absorption from polyethylene glycol (400 + 6000 (3 : 2)) suppositories in 4 male volunteers. The absorption was very poor from both preparations. It was concluded that the absorption of progesterone from suppositories in man cannot be enhanced by changing from adeps solidus to a polyethylene glycol vehicle.

In order to develop a rectal formulation of progesterone with a higher bioavailability than known so far, an enema consisting of progesterone dissolved in propylene glycol–povidone 90 (99 : 1) was prepared. The plasma concentrations obtained after administration of the enema and the adeps solidus suppositories were compared with those obtained after i.v. injection of progesterone dissolved in propylene glycol.

Materials and Methods

Materials

Progesterone Ph.Eur. grade (Mecobenzon, Denmark), [1,2,6,7-^{3}H]progesterone (spec. act. 87 Ci/mmol, toluene solution 1 mCi/ml, Amersham, U.K.), adeps solidus, propylene glycol Ph.Eur. grade (Mecobenzon, Denmark), povidone 90 (Kollidon 90, BASF) and PVC-suppository forms 1.15 ml (Supponova, Bang and Tegner, Denmark) were used for preparation of the enema and the suppositories.

Test preparation

One ml of an [1,2,6,7-^{3}H]progesterone–toluene solution was added to a solution of 130 mg progesterone in 1 ml chloroform. The solvent was evaporated by means of an air flow of argon and the residue dried in an oven at 80°C. The particle size of the progesterone ([^{3}H]progesterone) complied with the test for particle size described in the monograph for Guttae ophthalmicae, Ph.Eur. 2nd Edn.

For preparation of the suppositories the [^{3}H]progesterone was suspended in melted adeps solidus at about 40°C and moulded. Each suppository contained 10 mg of [^{3}H]progesterone. To prepare the enema the [^{3}H]progesterone was dissolved in propylene glycol and povidone 90 was added to give a final concentration of 1%. The enema contained 10 mg of [^{3}H]progesterone per ml. For i.v. injection a solution of the [^{3}H]progesterone in propylene glycol was prepared (10 mg/ml).

Experimental design

In a pre-experimental period 5 albino rabbits — their weights ranging from 1.95 to 2.21 kg — were accustomed to sit quietly in restraining boxes (pyrogen test boxes) for at least 6 h. The acceptance of the test preparations was secured by giving

inert suppositories and enemas stained with eosin in order to check any loss via the anus.

The suppositories or the enema were then given with one week's interval according to a randomized cross-over design to the 5 rabbits. They were fasted for 24 h before administration of the drug, but had free access to water.

The experiments were started in the morning. The rabbits were kept in restraining boxes during the first 6 h of the blood sampling period. The suppository was inserted just inside the internal sphincter and the enema administered about 5 cm from the anus using a rectal tube (identical with that used in Apozepam, A.L. Pharma, Norway). During the experiments it was controlled that there was no leaking from the anus. One rabbit had to be discarded, because the enema was discharged immediately after the application. Three weeks after the rectal administrations an i.v. injection was given to each rabbit the weights now ranging from 2.30 to 2.65 kg. The intravenous injection was given in the marginal ear vein. The administered dose of progesterone was always 5 mg/kg.

Blood samples of 0.5 ml were taken at appropriate times in heparinized test tubes from the ear not used for drug administration. Blood-plasma obtained after centrifu-

TABLE I

PLASMA CONCENTRATIONS, ABSORPTION CHARACTERISTICS AND BIOAVAILABILITY (MEAN ± S.E.) OF PROGESTERONE AFTER ADMINISTRATION OF VARIOUS DOSAGE FORMS TO RABBITS. C_{max} AND T_{max} ARE THE MEAN VALUES CALCULATED FROM THE INDIVIDUAL CURVES

Dose 5 mg/kg	i.v.	Rectal (supp.)	Rectal (enema)
Plasma concentration C [(μg/ml)$\times 10^2$] at t =			
0 min	10 ± 3	6 ± 1	11 ± 5
5 min	564 ± 49	–	–
10 min	584 ± 65	–	–
15 min	514 ± 58	23 ± 5	334 ± 62
20 min	510 ± 47	–	–
30 min	505 ± 57	40 ± 11	326 ± 43
45 min	465 ± 85	56 ± 30	326 ± 52
1 h	459 ± 66	69 ± 18	319 ± 50
1½ h	450 ± 79	77 ± 19	278 ± 42
2 h	395 ± 83	97 ± 18	283 ± 50
3 h	342 ± 53	75 ± 19	191 ± 34
6 h	226 ± 32	63 ± 19	86 ± 14
25½ h	132 ± 6	68 ± 10	34 ± 6
Number of rabbits	4	4	4
C_{max}	628 ± 80	82 ± 43 [a]	381 ± 108
T_{max} (h)	0.27 ± 0.28	1.75 ± 0.25 [a]	0.56 ± 0.32
$t_{1/2}$ (h)	5.10 ± 1.12		
AUC_{0-6h} [(μg/ml)$\times 10^2 \times$h]	2768 ± 1685	396 ± 210	1206 ± 370
$F_{\%}$	100	14 ± 8 [a]	44 ± 10

[a] Supp. vs. enema, $P < 0.05$.

gation was frozen until the time of analysis. The actual times of sampling are shown in Table 1.

Analysis

100 μl of plasma were transferred to 5 ml vials (BN Plastics, Chem. Instruments, Denmark) and discolorized by addition of 100 μl of concentrated hydrogen peroxide solution. 2.0 ml of Instagel (Packard, U.K.) were added to each sample which was stored at 5°C until the next day and then analyzed in a liquid scintillation counter (Beckman Model LS-250). The tests were made in duplicate. After correcting for background counts the data in counts per minute were converted to μg/ml by the use of standards.

Pharmacokinetic measurements

The observed plasma concentrations were plotted vs the time in a semilogarithmic system. The coordinates (time, ln C) from 0 to 6 h obtained after the i.v. administration were tested for linearity. The C_{max} and the T_{max} were determined from the individual curves of each rabbit.

In order to determine the systemic availability (F%) of the two rectal dosage forms, the areas under the plasma concentration curves (AUC) from t = 0 to t = 6 h were estimated according to the trapezoidal rule and compared with that of the i.v. administration. The systemic availability as expressed by Eqn. 1 was calculated.

$$F\% = \frac{AUC_{(enema/suppositories)}}{AUC_{intravenous}} \times 100 \qquad (1)$$

Statistics

Statistical analyses were performed with Student's paired *t*-test. Tests for normality of the data were carried out according to Lilliefors (1967) and for equal variances by an *F*-test. Because of the discrete distribution pattern of T_{max} the Wilcoxon rank-test was used for comparison of the T_{max} values.

Results and Discussion

The main purpose of the study was to determine the systemic availability of micronized progesterone in adeps solidus suppositories compared with that of progesterone dissolved in a propylene glycol–povidone 90 (99 : 1) enema. The results obtained are shown in Table 1. Fig. 1 shows the mean plasma concentration–time curves obtained after administration of progesterone 5 mg/kg given as a single i.v. dose, a suppository and an enema to 4 rabbits.

As can be seen from Fig. 1 the administration of the enema causes a much higher plasma concentration and an earlier peak than the suppositories. The mean plasma peak concentration (C_{max} = 3.81 ± 1.08 μg/ml; mean ± S.E.) was reached within about half-an-hour (T_{max} = 0.56 ± 0.32 h) for the enema, whereas the C_{max} (0.82 ± 0.43 μg/ml) for the suppositories was not reached until after about 2 h (T_{max} = 1.75

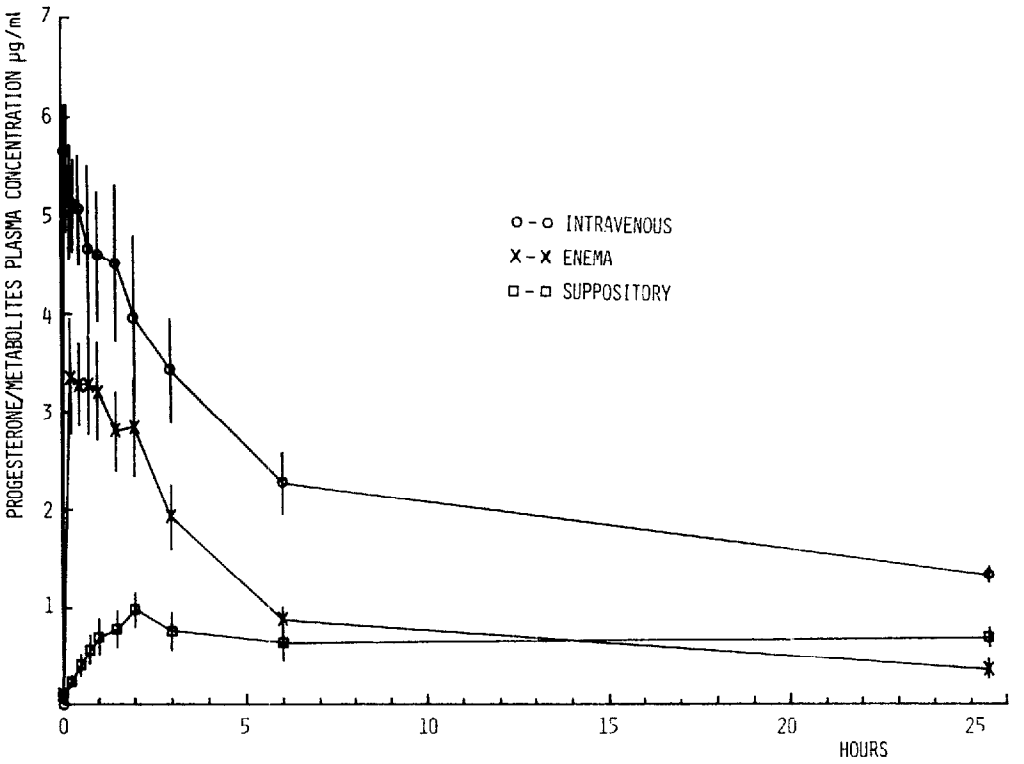

Fig. 1. Plasma concentration–time curves of progesterone/metabolites after administration of 5 mg/kg in various dosage forms to 4 rabbits. Each point represents the mean plasma concentration ± S.E.

± 0.25 h). Compared with the intravenous injection C_{max} for the suppositories is less than one-seventh of C_{max} (6.28 ± 0.80 µg/ml) after intravenous injection.

The decline of the mean plasma concentration curve obtained after i.v. administration shows a linear course from 0 to 6 h in a semilogarithmic plot, the correlation coefficient of the plot being 0.993. The elimination coefficient of this phase was 0.150 h^{-1}. The mean plasma half-life determined from the individual curves was 5.10 ± 1.12 h for the total of progesterone and its metabolites.

The declining phase of all 3 plasma concentration curves shows an almost horizontal course after 6 h, indicating that a relatively high capacity compartment is involved in the disposition of progesterone and its metabolites. The different slopes of the i.v. curve between 0 and 6 h and after 6 h confirm that the progesterone elimination kinetics corresponds to a multicompartment model.

The systemic availability of the suppositories and the enema (F%) was 14 and 44%, respectively, and was found to differ significantly ($P < 0.05$). The values of C_{max} and AUC_{0-6h} obtained with the two rectal dosage forms were also significantly different ($P < 0.05$).

It should be stressed that from this study nothing can be said about the total availability ($AUC_{0-\infty}$) of progesterone from the two dosage forms as the residual area ($AUC_{6-\infty}$) was not determined. In most clinical situations, however, the systemic availability within 6 h is essential for the therapeutic value of the drug.

It should also be noticed that progesterone in this study was determined by measuring the total radioactivity, i.e. progesterone and its metabolites and not only the parent compound. Therefore the results do not give an answer to the question to which extent the first-pass metabolism of progesterone can be avoided by rectal administration.

The marked difference in bioavailability of the two rectal dosage forms, suppository and enema, has been observed for several drugs such as diazepam (Knudsen, 1977), paracetamol (Moolenaar et al., 1979a and b) and theophylline (Truitt et al., 1950; Rassing, 1976).

The results obtained in the present animal study encourage further research with the aim of optimizing the vehicle in rectal dosage forms containing lipophilic drugs.

Acknowledgement

The skillful technical assistance of Ms. Elly Jørgensen is greatly appreciated.

References

Brotherton, J., Sex Hormone Pharmacology. Metabolism of Naturally Occurring Steroids, Academic Press, London-New York-San Francisco, 1976, pp. 101–105

Knudsen, F.U., Plasma-diazepam in infants after rectal administration in solution and by suppository, Acta Paediatr. Scand., 66 (1977) 563–567

Lilliefors, H.W., On the Kolmogorov-Smirnov test for normality with mean and variance unknown, Am. Statist. Ass. J., 18 (1967) 399–402

Moolenaar, F., Olthof, L. and Huizinga, T., Biopharmaceutics of rectal administration of drugs in man. 3. Absorption rate and bioavailability of paracetamol from rectal aqueous suspensions, Pharm. Weekbl. Sci. Edn., 1 (1979a) 25–30

Moolenaar, F., Schoonen, A.J.M., Everts, A. and Huizinga, T., Biopharmaceutics of rectal administration of drugs in man. 4. Absorption rate and bioavailability of paracetamol from fatty suppositories, Pharm. Weekbl. Sci. Edn., 1 (1979b) 89–94

Nillius, S.J. and Johansson, E.D.B., Plasma levels of progesterone after vaginal, rectal or intramuscular administration of progesterone, Am. J. Obstet. Gynecol., 110 (1971) 470–477

Rassing, M., Lægemiddelformulering og rektal absorption, Ph.D. thesis, Department of Pharmaceutics, Royal Danish School of Pharmacy, Copenhagen, 1976

Rassing, M., Release and absorption of progesterone from rectal dosage forms, FIP 1979 Abstr., p. 40

Truitt, E.B., Jr., McKusick, V.A. and Krantz, J.C., Theophylline blood levels after oral, rectal and intravenous administration, and correlation with diuretic action, J. Pharmacol. Exp. Ther., 100 (1950) 309–315