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Exploratory studies on the in vitro release and bioavailability of dextropropoxyphene from lipophilic and hydrophilic suppositories

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Summary

The rectal bioavailability of propoxyphene has been investigated in an explorative study on six volunteers after administration of hydrophilic and lipophilic suppositories with and without a mucoadhesive. A tablet formulation was used as reference. The in vitro dissolution characteristics of the four different rectal compositions were studied by using the basket, paddle and flow-through techniques in order to determine whether these methods could be used to predict the plasma concentration vs time curves. The results indicate that rectal administration of dextropropoxyphene napsylate reduces first-pass elimination of the drug. By choosing a hydrophilic suppository base it was possible to achieve the same rate of absorption and a 60% greater extent of bioavailability of propoxyphene than after oral administration. The basket method was the most suitable technique to predict a ranking between the different compositions.

Introduction

Dextropropoxyphene (P) is a well known analgesic used alone or in combination with other analgesic agents for the treatment of mild to moderate pain. Oral administration of P reduces systemic bioavailability due to first-pass elimination varying from 30 to 70% among individuals with an average of about 60% compared to intravenous administration (Perrier and Gibaldi, 1972). It cannot generally be stated that the rectal route always results in improved bioavailability compared to oral administration of high liver-clearance drugs. One reason is that the first-pass effect might instead be due to gut wall metabolism. Another reason is of course that the extent of absorption is reduced. For diazepam,

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Abbreviations: P, dextropropoxyphene napsylate/dextropropoxyphene/propoxyphene; NP, norpropoxyphene; HYD, hydrophilic suppository; HYDMUC, hydrophilic suppository with mucoadhesive; LIP, lipophilic suppository; LIPMUC, lipophilic suppository with mucoadesive.

lidocaine and morphine (De Boer and Breimer, 1979; Moolenaar et al., 1980, 1985), it has been shown that an increased extent of bioavailability in humans is obtained after rectal administration. The reason for this might be that the upper rectum drains via the portal venous system to the liver while the veins from the lower rectum are drained via the vena cava to the systemic circulation, thereby avoiding first-pass elimination (Steed et al., 1989). It must be emphasized that the region between the two areas is extensively anastomosed. It is probable that the composition of a rectal dosage form is of great importance for the degree of spreading towards the proximal part of the rectum, and thus for the extent of avoidance of hepatic first-pass metabolism. For example, an enema was shown to spread more extensively than a lipophilic suppository (Jay et al., 1985; Hardy et al., 1986). A recently proposed idea is to attempt to fix the dosage form in the lower part by using a mucoadhesive substance. For example, positive results were reported by Hosny (1988) in a study where a composition of polyethylene glycol and polycarbophil in a sustained release suppository of ketoprofen was administered to dogs and humans.

The aim of the present explorative studies was to study the rectal absorption rate and bioavailability of P after administration of different suppository compositions. In addition, the dissolution characteristics of the different compositions were investigated by using the basket, paddle and flow-through techniques in order to ascertain whether the use of these techniques was feasible for predicting the in vivo plasma concentration data vs time profiles.

Materials and Methods

Chemicals

The following chemicals were used in the different formulations: dextropropoxyphene napsylate, B.P. (Eli Lilly, U.K.); Adeps solidus, Ph. Eur. (Witepsol H12, Dynamit Nobel Chem., Germany); Paraffinum liquidum, Ph. Eur. (Witco BV, The Netherlands); polyethylene glycol ointment 1500, DAB 8 (BP Chem. Ltd, U.K.); polyethylene glycol 3350, DAB 8 (BP Chem. Ltd, U.K.); and Carbopol EX-55 (polycarbophil, BF Goodrich, U.S.A.).

TABLE 1

Complete composition of the dextropropoxyphene napsylate (P) suppositories tested in vitro and in vivo

Composition abbreviation	P (mg)	Suppository base		Mucoadhesive (mg)/(%) [a]	Total weight (g) [b]
		PEG (g)	Witepsol (g)		
HYD	100 [c]	2.580			2.68
HYDMUC	100	2.553		27/1.0	2.68
LIP	100		2.180		2.28
LIPMUC	100		2.020	160/7.0	2.28

[a] Per cent mucoadhesive of total suppository weight.
[b] The volumes of the hydrophilic and lipophilic suppositories are equal.
[c] 1.8×10^{-4} mol.

Physico-chemical properties of dextropropoxyphene napsylate

The following parameters were used for dextropropoxyphene napsylate: log D 2.36, octanol-water (pH 7.4) (Hansch et al., 1987); solubility (phosphate buffer pH 7.4 (USP), 37°C), 2.0 mg/ml; and pK_a 9 (Melin et al., 1979).

Solid systems tested

The suppository compositions investigated are shown in Table 1 with the corresponding abbreviations. The drug substance was partially dissolved, partly suspended in both the hydrophilic dissolving base (PEG) and the lipophilic melting base (Witepsol). Sieve analysis showed that 72% of dextropropoxyphene napsylate had a particle size smaller than 125 μm. One composition of each type contained Carbopol Ex-55 for which the mucoadhesive properties have been reported elsewhere (Dyvik and Graffner, 1992). The amount of mucoadhesive chosen was based on in vitro dissolution results and the feeling of adhesion holding a wetted suppository between two fingers for a defined time period. The suppositories were produced manually on a small scale by homogenizing dextropropoxyphene napsylate (P) into the melted base. In order to obtain a homogeneous blend of the bioadhesive agent in HYD-

MUC, it was necessary to mix the powder with the PEG before melting. For LIPMUC the polycarbophil was added before the active substance. The melt was poured into moulds of stainless steel, and allowed to cool at room temperature. 120 suppositories were moulded on each occasion and excess base was scraped off after solidification. The weights of 20 individual suppositories were checked and found to be within $\pm 5\%$ of the theoretical weight. Before moulding suppositories of the hydrophilic type, it was necessary to lubricate the moulds with liquid paraffin. The Dexofen™ tablet 100 mg was taken from the regular production line (Astra Läkemedel AB, Sweden).

In vitro dissolution techniques

The in vitro dissolution rate of P from the suppositories was examined by means of the basket (Apparatus I, USP XXII), paddle (Apparatus II, USP XXII) and flow-through methods (Apparatus IV, USP XXII) (Langenbucher et al., 1983; Möller, 1983; Gjellan and Graffner, 1989; Nicklasson and Langenbucher, 1990; US Pharmacopeia, 1991).

Deaerated phosphate buffer (USP) (pH 7.4; 37 ± 0.5°C) was used as a dissolution medium in all cases. The beaker methods (Sotax AT 6, Sotax AG, Switzerland) required 900 ml and samples (5 ml) of test solution were collected manually after 5, 10, 20, 30, 45, 60 and 90 min for hydrophilic suppositories and after 5, 10, 30, 60, 90, 120, 180, 240 and 300 min for lipophilic suppositories. In Apparatus II a stainless-steel net (mesh width = 1 mm) was placed between the paddle and the suppository and a metal helix was mounted around this to prevent it from floating up to the surface of the dissolution medium. The speed of rotation of the paddles was 50 rpm. Apparatus I was used unmodified at a rotation speed of 100 rpm, and the mesh width of the basket was 40 mesh. The flow-through cells used (Disotest/Dissotest CY, Sotax AG, Switzerland) had a diameter of 12 mm and non-circulated buffer at a flow rate of 16 ml/min was used. For LIPMUC, a flow rate of 8 ml/min was also examined in an attempt to prevent clogging of the filter by the swelling polymer which occurred at 16 ml/min. The dissolution tests were performed with six separate dosage units for each technique.

The amount of dissolved P was detected spectrophotometrically at 275 nm. The amount of P released from lipophilic suppositories was detected by a validated HPLC method with UV detection at 214 nm due to the relatively slow release rate which resulted in low concentrations.

In vivo study design

Six healthy Caucasian males (three) and females (three) aged 24–35 years (mean = 31) of weight range 55–76 kg (mean = 69) were included in the study. All were healthy according to medical history, physical examination, and blood and urine analyses. The volunteers were informed both orally and in writing about the aim of the study and about possible risks according to the Helsinki declaration. After this information they gave their signed consent to participate in the study.

The trial was carried out according to a randomized cross-over design, and was performed at St. Göran's Hospital, Stockholm, Sweden. It was approved by the Ethics committee at Södersjukhuset, Stockholm, Sweden. Each volunteer received a dose of 100 mg on five separate occasions at weekly intervals. A micro enema (Klyx, Ferring) was administered about 1 h before each application except for the tablet in order to standardise the experimental conditions. Any defecation within 6 h was recorded. The volunteers fasted 8 h before and 3 h after administration, whereupon a standardized meal was given. They stayed at the study unit during the first 11 h of the study. No other medicine or alcohol were allowed 24 h prior to or during each trial day.

Venous blood specimens were collected immediately before and 30, 60, 90, 120 and 150 min and 3, 5, 8, 11, 24, 28, and 32 h after drug administration. The samples were centrifuged within 1 h and the plasma separated and stored at -20°C pending analysis. Assays of P and the main metabolite norpropoxyphene (NP) in plasma were performed by a validated HPLC method (Pettersson and Nilsson, 1992). The instrumental limit of detection and limit of quantification was

2 nM for both compounds at a plasma volume of 1.0 ml.

Calculations

The maximum plasma concentrations of P and NP (C_{max}) and the time to reach C_{max} (T_{max}) were estimated for each volunteer. The overall elimination rate constant, β, was determined by linear regression analysis of the terminal linear part of the log plasma concentration vs time curve. The biological half-life, $t_{1/2}$, was calculated from $\ln 2/\beta$. The area under the plasma concentration vs time curves, AUC, was calculated using the trapezoidal rule from time 0 to the time at which C_{max} was attained. The logarithmic trapezoidal rule was applied to the declining part of the curve in order to increase the accuracy of the AUC estimate. The remaining area was obtained from the ratio between the concentration at time T_n, as calculated from the regression line, and the elimination rate constant. The total area under the curve, AUC_{tot}, was obtained by summation of the areas. Per cent rest area was calculated by determining the relation between the estimated remaining area ($T_n \rightarrow \infty$) and the total area under the curve.

The relative extent of bioavailability (F_{rel}) of P from the suppositories was estimated from the ratio between the AUC_{tot} of the suppository and that of the tablet (Gibaldi, 1984).

The mean residence time (MRT) was calculated using the relationship $MRT = AUMC/AUC_{tot}$, where AUMC corresponds to the area under the first moment curve (Gibaldi, 1984). MDT in vitro was evaluated by calculating the area between the ordinate (y) of the plotted cumulative percentage dissolved and the level indicating 100% dissolved. If 100% of the drug was not dissolved during the dissolution experiment, the tail of the curve was estimated based on an exponential model. The pharmacokinetic analysis was processed on Digital Vax computers and written in the RS/1 command language (BBN Software Products Corp.).

Statistical methods

Descriptive statistics were applied to describe the in vitro dissolution profiles and the plasma concentration profiles of the different compositions. Nonparametric methods (Lehmann, 1975) were used to analyse the pharmacokinetic parameters, since they are free from the assumption that the population distribution follows a specific parametric distribution. A paired comparison of the pharmacokinetic parameters was carried out between the suppositories and the tablet. The Wilcoxon Sign Rank tests and an estimate of the relative extent of bioavailability with a 95% confidence interval based on the Wilcoxon Signed Rank statistic were calculated. Statistical significance was declared for an outcome with a p value less than or equal to 0.05. The SAS system under VMS™ was used when analysing the data.

Results

In vitro release

In vitro dissolution profiles from the compositions are shown in Fig. 1a–c. It is obvious that the release pattern of P from the four different suppositories is dependent both on the composition and on the dissolution technique.

Type of base

HYD releases 100% of P within 30–60 min. The standard deviation is below 2 units in the paddle and basket and below 5 in the flow-through cell. The suppository decreases gradually in size during the dissolution test and disintegration of the suppository is limited.

LIP releases P more slowly compared to HYD and a greater variation in data is observed. Only approx. 50% is detected after 300 min. LIP melts, disintegrates and spreads due to the temperature of the medium and the agitation in the technique used. The standard deviation is maximally 12% for the flow-through cell. For the paddle and basket, the variation is less than 5.5 units.

Presence of polycarbophil

The content of polycarbophil in the hydrophilic suppository causes extended release. The mucoadhesive produces a thin gel layer when exposed to the buffer and this is observed visually

during the dissolution test. The addition of polycarbophil to the lipophilic suppositories produces more effective spreading of the fat and a porous structure is seen.

In vitro technique

HYD and HYDMUC produce the same behaviour in all three dissolution techniques used. For LIP and LIPMUC, however, different be-

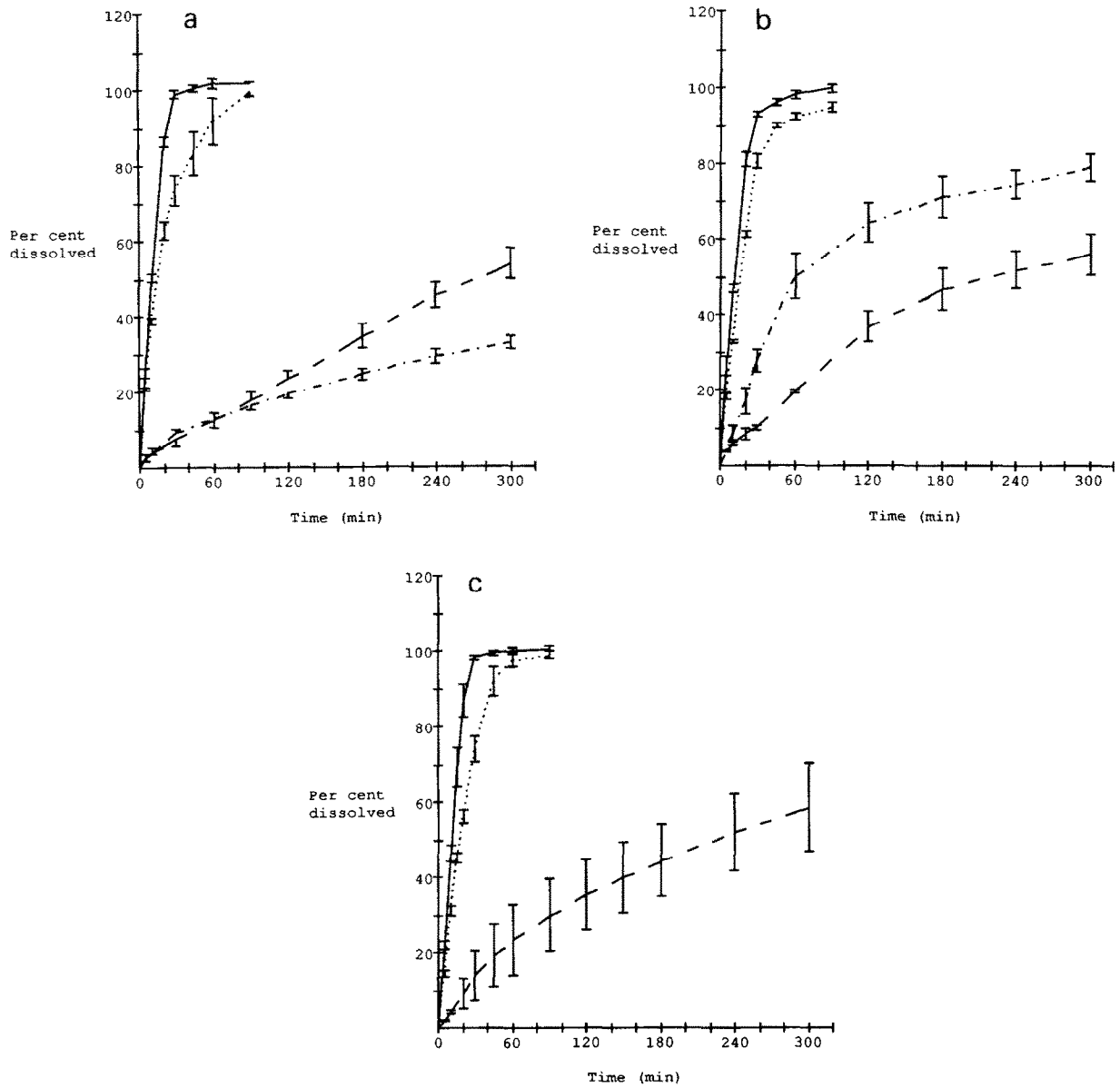

Fig. 1. Mean in vitro dissolution data of propoxyphene ($n = 6$) from HYD (———), HYDMUC (· · · · · ·), LIP (— — —) and LIPMUC (· – · – ·) using the (a) basket, (b) paddle and (c) flow-through techniques. Error bars correspond to standard deviations.

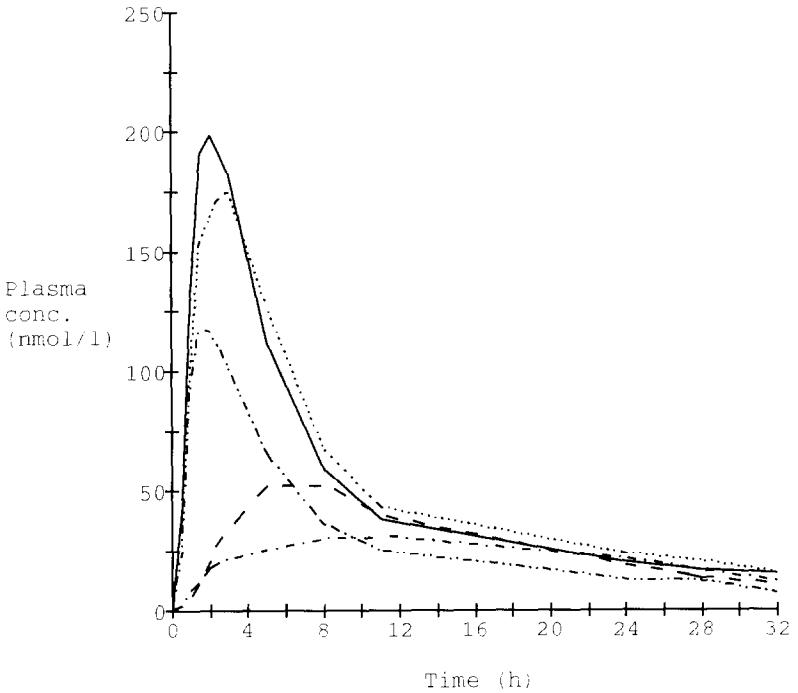

Fig. 2. Average plasma concentration data ($n = 6$) vs time of propoxyphene after administration of tablet (– · · –), HYD (———), HYDMUC (· · · · · ·), LIP (— — —) and LIPMUC (· – · – ·).

haviour is observed among the techniques. In the paddle LIP melts and remains under the net continuously releasing small fat drops to the surface. LIPMUC's more porous structure causes greater dispersion under the net which indicates a larger contact area and a more rapid release rate. In the basket most of the melted base of LIP remains within the basket during the entire test. This is also seen for LIPMUC, however, the swelling of polycarbophil resulted in a visible barrier to diffusion. Due to different spreading behaviour P is released more rapidly from LIP

TABLE 2

Mean pharmacokinetics ($n = 6$) of propoxyphene (standard deviations within parentheses)

Treatment	C_{max} (nmol/l)	T_{max} (h)	MRT (h)	$T_{1/2}$ (h)	AUC_{tot} (nmol/l per h)	Rest area (%)	F_{rel}	F_{rel} (95% c.i.)
Tablet	138	2.3	17.9	16.0	1239	24.5		
	(75)	(0.9)	(5.3)	(6.4)	(428)	(7.2)		
HYD	213	2.1	17.1	14.9	1930 [a]	16.4	1.6	(1.04, 2.29)
	(94)	(0.6)	(3.4)	(1.9)	(606)	(4.4)	(0.4)	
HYDMUC	185	2.9	17.4	14.8	2026 [a]	17.1	1.6	(1.23, 2.68)
	(91)	(1.2)	(3.0)	(1.8)	(640)	(3.5)	(0.5)	
LIP	58 [a]	7.0 [a]	19.5	12.7	1099	18.1	0.9	(0.57, 1.29)
	(19)	(2.5)	(3.6)	(3.6)	(615)	(5.8)	(0.3)	
LIPMUC	40 [a]	10.3	20.1	10.1	903 [a]	22.2	0.7	(0.20, 0.88)
	(20)	(7.4)	(5.4)	(3.6)	(525)	(5.5)	(0.3)	

[a] Statistically significantly different from the tablet ($p = 0.03$).

than LIPMUC in the basket and vice versa in the paddle. In the flow-through method LIPMUC clogged the filter. The problem still arose when testing a flow rate of 8 ml/min.

Plasma concentrations and bioavailability

Tolerance of suppository base

One volunteer experienced a burning feeling at the application site and a painful defecation urge after administration of HYD. None of the other subjects reported similar events.

Propoxyphene

The mean plasma concentrations of P are presented in Fig. 2. The pharmacokinetic data are listed in Table 2.

A mean increase of 54% in C_{max} is indicated after administration of HYD compared to the tablet, however, the difference is not statistically significant. The values of T_{max}, $T_{1/2}$ and MRT of the tablet and HYD are similar. HYD results in a statistically significantly higher AUC_{tot} than the tablet ($p = 0.03$). The 95% confidence interval of the mean relative bioavailability from HYD is (1.04, 2.29). One is not included in the interval which means that the extent of bioavailability from HYD is significantly higher than that from the tablet.

LIP produces a significantly lower C_{max} and a later T_{max} than the tablet. The mean peak attained was thus 42% of that of the tablet. The AUC_{tot} is not significantly separated compared to the tablet, and the confidence interval of F_{rel} is (0.57, 1.29) with 1.0 included.

The addition of a mucoadhesive does not influence the conclusions based on the plain hydrophilic base. However, the 95% confidence interval of F_{rel} of HYDMUC is (1.23, 2.68) which deviates further from 1.0 than for HYD. Furthermore, there is a tendency towards a lower mean C_{max} (185 vs 213 nmol/l) and a later mean T_{max} when comparing the pharmacokinetics of HYD and HYDMUC. The data for LIPMUC do not

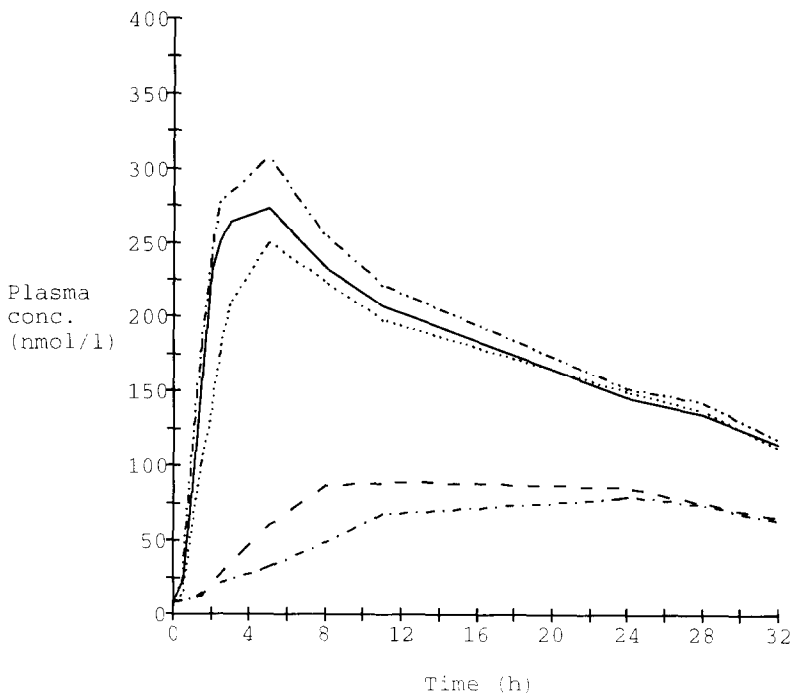

Fig. 3. Average plasma concentration data ($n = 6$) vs time of norpropoxyphene after administration of tablet (–··–), HYD (———), HYDMUC (·····), LIP (— — —) and LIPMUC (·–·–·).

TABLE 3

Mean pharmacokinetics (n = 6) of norpropoxyphene (standard deviations within parentheses)

Treatment	C_{max} (nmol/l)	T_{max} (h)	$T_{1/2}$ (h)	AUC_{tot} (nmol/l per h)	Rest area (%)
tablet	338	3.9	23.7	9995	39.2
	(86)	(1.2)	(2.9)	(2530)	(3.6)
HYD	302	3.8	25.5	10076	42.2
	(64)	(1.4)	(6.9)	(2270)	(9.2)
HYDMUC	258	6.1	24.4	9390	41.3
	(79)	(3.0)	(12.4)	(2155)	(13.6)
LIP	99	13.8	30.4	5044	48.4
	(45)	(8.0)	(24.6)	(2490)	(17.2)
LIPMUC	82	19.7	26.5	4085	51.1
	(42)	(6.7)	(13.4)	(1955)	(15.4)

differ from those of LIP, although the same tendency towards a lower mean C_{max} and later mean T_{max} is also seen for LIPMUC.

Norpropoxyphene

The mean plasma concentration data of NP are presented in Fig. 3. In Table 3 the mean pharmacokinetic data are reported.

The highest C_{max} is reached after administration of the tablet. The T_{max} is the same for the tablet and HYD, while the time is delayed for the other suppository formulations. The total area under the plasma concentration curve is estimated to be the same for the tablet and the hydrophilic compositions.

Association between in vitro dissolution data and in vivo plasma concentration data

The in vivo plasma concentration data show a marked difference between the suppository formulations as illustrated by both a lower rate of absorption and a reduction in the extent of bioavailability from the lipophilic compositions. Thus, P is not available for absorption to the same extent from the lipophilic unit. The addition of a mucoadhesive does not have any significant effect on the pharmacokinetics even though there is a tendency towards more delayed absorption from both HYDMUC and LIPMUC.

All techniques showed the same large in vitro difference between the hydrophilic and lipophilic compositions. The same ranking between all four suppositories is obtained based on the in vitro dissolution profiles using the basket method. However, the paddle technique ranks HYD and HYDMUC in the correct manner but not LIP and LIPMUC.

The MRT values of P from the different suppository compositions were plotted vs the MDT in vitro determined by using the basket and paddle methods. The regression lines, were calculated to be $y = 0.19x + 17.45$ ($r^2 = 0.851$; MSE = 0.50) and $y = 0.32x + 17.57$ ($r^2 = 0.577$; MSE = 1.42), respectively.

Discussion

In vitro dissolution tests

The basket and paddle techniques are found to be technically applicable for studying drug release from the set of rectal compositions investigated. The use of the flow-through cell is limited since the amount of mucoadhesive in LIPMUC prevents testing at standard flow rates (8 and 16 ml/min). The influence of an even lower flow rate must be investigated.

The basket, paddle and flow-through techniques result in similar dissolution profiles of P from the hydrophilic suppositories. This is probably explained by the successive reduction in size during dissolution which is independent of the surrounding hydrodynamics.

The melting suppositories deform and spread, and the different techniques allow for different kinds of spreading and consequently, for different in vitro release patterns. The paddle allows the drug to be more freely dispersed than the basket and this might be the reason why the ranking of LIP and LIPMUC based on dissolution profiles is different. The spreading volume is limited in the basket which presents a greater barrier due to the swelling polymer. In the paddle the drug substance diffuses more freely to the interface of the melted base and the media, when containing a swelling mucoadhesive.

Fig. 1 illustrates the variation in data with error bars representing the standard deviation. It can be seen that the hydrophilic suppositories

give more consistent results than the lipophilic suppositories. The variation in dissolution rate from LIP is compared among the three different techniques and it is evident that the flow-through cell causes the greatest variation. This is most probably due to the different spreading in the flow-through cell compared to in the beakers.

Bioavailability

Rectal administration of P reduces the first-pass elimination of the drug. It is apparent that the insertion of the hydrophilic dissolving suppository increases the extent of bioavailability of P. The base releases P at a rate which leads to the same rapid absorption as in the case of oral administration, however, the peak concentrations of P are significantly higher. The rectal dose in a hydrophilic base should consequently be reduced to achieve the same plasma concentrations of P as after oral administration.

From the present explorative investigation, it is impossible to conclude whether an increased extent of bioavailability is also reached after administration of the lipophilic suppositories. The comparatively lower absorption rate produced might be due to the high affinity of P to the lipophilic base which is also evident from the partition coefficient (Hansch et al., 1987).

The addition of a mucoadhesive agent does not appear to produce a further increase in the extent of bioavailability of P. Since a gamma-scintigraphic study was not performed simultaneously, it is impossible to judge whether the amount of polycarbophil used was sufficient to fix the suppository in the lower rectum. There are, however, indications that the polymer delays the release from both the lipophilic and hydrophilic compositions.

Several samples taken at time 0 contained NP when P had been administered the week before. No preference was noted for any composition. The highest concentration observed at time zero was 28 nmol/l which contributed 0.2% to the total area under the curve. It is probable that the explorative design utilizing six volunteers and the plasma sampling time of 32 h is unsuitable for rectal comparisons. It is recommended that pharmacokinetic calculations should be based on a sampling of plasma until at most 10% of the maximum concentration is reached. This was attained in the case of P but not NP. Gram et al. (1979) showed that blood sampling for 72 h was necessary to achieve a plasma concentration of NP at 10% of the maximal concentration after administration of 65 mg dextropropoxyphene HCl. However, the biological half-life determined for P and NP after administration of the tablet and the suppositories is within the same range as that reported by Brøsen et al. (1985), Gram et al. (1979) and Girre et al. (1991).

Conclusions

Rectal administration of P reduces the first-pass elimination of the drug. By choosing a hydrophilic suppository base it is possible to achieve a similar rate of absorption and a 60% higher extent of bioavailability of dextropropoxyphene than after oral administration. The addition of a mucoadhesive agent does not seem to produce any further improvement. The base is critical for the absorption and a hydrophilic type is preferable. The basket technique is more suitable than the paddle and flow-through techniques, to predict a ranking between different suppository compositions.

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References

Brøsen, K., Gram, L.F., Schou, J., Larsen, N.E. and Thayssen, P., Dextropropoxyphene kinetics after single and repeated oral doses in man. *Eur. J. Clin. Pharmacol.*, 29 (1985) 79–84.

De Boer, A.G. and Breimer, D.D., Drug absorption: Portal or systemic? In Prescott, L.F. and Nimmo W.S. (Eds), *Pro-*

ceedings of the Edinburgh International Conference, ADIS Press, Sydney, Australia, 1979, pp. 61–72.

Dyvik, K. and Graffner, C., Investigation of the applicability of a tensile testing machine for measuring mucoadhesive strength. *Acta Pharm. Nord.*, 4 (1992) 79–84.

Gibaldi, M., *Biopharmaceutics and Clinical Pharmacokinetics*, Lea & Febiger, Washington, 1984, pp. 17–28, 131–155

Girre, C., Hirschhorn, M., Bertaux, L., Palombo, S., Dellatolas, F., Ngo, R., Moreno, M. and Fournier, P.E., Enhancement of propoxyphene bioavailability by ethanol. Relation to psychomotor cognitive function in healthy volunteers. *Eur. J. Clin. Pharmacol.*, 41 (1991) 147–152.

Gjellan, K. and Graffner, C., Comparative dissolution studies of rectal formulations using the basket, the paddle and the flow-through methods: I. Paracetamol in suppositories and soft gelatine capsules of both hydrophilic and lipophilic types. *Acta Pharm. Nord.*, 1 (1989) 343–354.

Gram, L.F., Schou, J., Way, W.L., Heltberg, J. and Bodin, N.O., d-Propoxyphene kinetics after single oral and intravenous doses in man. *Clin. Pharmacol. Ther.*, 26 (1979) 473–482.

Hansch, C., Björkroth, J.P. and Leo, A., Hydrophobicity and Central nervous system agents: On the principal of minimal hydrophobicity in drug design. *J. Pharm. Sci.*, 76 (1987) 663–687.

Hardy, J.G., Wood, E., Clark, A.G. and Reynolds, J.R., Colonic motility and enema spreading. *Eur. J. Med.*, 12 (1986) 176–178.

Hosny, E.A., Rectal drug delivery using a bioadhesive containing dosage form. Dissertation, University of Wisconsin, Madison, 1988.

Jay, M., Beihn, R.M., Digenis, G.A., Deland, F.H., Caldwell, L. and Mlodozeniec, A.R., Disposition of radiolabelled suppositories in humans. *J. Pharm. Pharmacol.*, 37 (1985) 266–268.

Langenbucher, F., In vitro drug release from suppositories: Flow-through method. In Glas, B. and De Blaeye. C.J. (Eds), *Rectal Therapy; Proceedings of the Symposium on the Advantages and Problems Encountered in Rectal Therapy*, Saint Remy de Provence, 1984, pp. 103–104.

Lehmann, E.L. *Nonparametrics: Statistical Methods Based on Ranks*, Holden-Day, San Francisco, 1975.

Melin, A.T., Ljungcrantz, M. and Schill, G., Reversed-phase ion-pair cromatography with an adsorption stationary phase and a hydrophobic quaternary ammonium ion in the mobile phase: I. Retention studies with tetrabutylammonium as cationic component. *J. Chromatogr.*, 185 (1979) 225–239.

Moolenaar, F., Bakker, S., Visser, J. and Huizinga, T., Biopharmaceutics of rectal administration of drugs in man: IX. Comparative biopharmaceutics of diazepam after single rectal, oral intramuscular and intravenous administration in man. *Int. J. Pharm.*, 5 (1980) 127–137.

Moolenaar, F., Yska, J.P., Visser, J. and Meijer, D.K.F., Drastic improvement in the rectal absorption profile of morphine in man. *Eur. J. Clin. Pharmacol.*, 29 (1985) 119–121.

Möller, H., Dissolution testing of different dosage forms using the flow through method. *Pharm. Ind.*, 45 (1983) 617–622.

Nicklasson, M. and Langenbucher, F., Description and evaluation of the flow cell dissolution apparatus as an alternative test method for drug release. *Pharmacopeial Forum*, May–June (1990) 532–540.

Perrier, D. and Gibaldi, M., Influence of first-pass effect on the systemic availability of propoxyphene. *J. Clin. Pharmacol.*, 12 (1972) 49–52.

Pettersson, K.-J. and Nilsson, L.B., Determination of dextropropoxyphene and norpropoxyphene in plasma by high-performance liquid chromatography. *J. Chromatogr.*, 581 (1992) 161–164.

Steed, K.P., Wilson, C.G. and Washington, N., Drug delivery to the large intestine. In Wilson, C.G. and Washington, N. (Eds), *Physiological Pharmaceutics. Biological Barriers to Drug Absorption*, Ellis Horwood, Chichester, 1989, pp. 91–108.

US Pharmacopeia, 22nd Revision, Suppl. 5, 1991, p.2713.