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Research Paper

The Talinolol Double-Peak Phenomenon Is Likely Caused by Presystemic Processing After Uptake from Gut Lumen

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Purpose. Evaluation of the double-peak phenomenon during absorption of the β_1-selective blocker talinolol relative to paracetamol, which is well absorbed from all parts of the gut, and relative to vitamin A, which is absorbed via the lymphatic pathway.
Methods. Talinolol was given with paracetamol and retinyl palmitate in fast-disintegrating, enteric-coated, and rectal soft capsules to 8 fasting male healthy subjects (21–29 years, 68–86 kg). To evaluate whether the talinolol double-peak is associated with processes of food absorption, a breakfast was served 1 h after administration of a fast disintegrating capsule.
Results. Bioavailability of talinolol in enteric-coated and rectal capsules was significantly reduced by about 50% and 80%, respectively, despite unchanged bioavailability of paracetamol. Double-peaks appeared after 2–3 h and 4–6 h with talinolol given as fast-liberating capsules. Food increased the maximum concentrations significantly (223 ± 76 μg/ml vs. 315 ± 122 μg/ml, $p < 0.05$) and shifted the second peak of talinolol to shorter t_{max} values (3.8 ± 1.2 h vs. 2.1 ± 0.6 h, $p < 0.05$), which was associated with faster absorption of retinyl palmitate. Pharmacokinetic model fits showed that about half of the oral talinolol dose given with and without meal is drained from the intestine via a presystemic storage compartment.
Conclusions. The double-peak phenomenon of talinolol is likely caused by a presystemic storage compartment, which represents the complex interplay of heterogeneous uptake and kick-back transport processes along the intestinal-hepatic absorption pathway.

KEY WORDS: double-peak phenomenon; pharmacokinetics; talinolol.

INTRODUCTION

Absorption of drugs from the gastrointestinal tract is a complex process the variability of which is influenced by many physicochemical and physiologic factors (1,2). Several structurally diverse drugs with adequate lipid solubility like celiprolol, pafenolol, acebutolol, cimetidine, danazol, and veralipride are slowly, erratically, and incompletely absorbed from the gastrointestinal tract generating double or multiple peaks or even plateau-like plasma concentrations-time profiles as caused by modified release formulations (3–9). One well-characterized example is the nonmetabolized β_1-adrenergic blocker talinolol (weak base; pK_a 9.4; log D = 1.1; high water solubility at acidic pH, 4.5 g/L at pH 7.0; absolute bioavailability in man, 55–70%), which shows distinct maximums of the serum concentration-time curve 1–2 and 4–6 h after oral administration (10).

Deeper insight into the physiologic mechanisms for erratic and delayed absorption could generate novel concepts to improve extent and to control rate of absorption of drugs with deficiencies in bioavailability.

The following mechanisms cause erratic absorption: enterohepatic circulation, fractionated gastric emptying, and separated "absorption windows" along the intestinal tract (11–13). However, talinolol undergoes only minor enterohepatic recirculation (14). Furthermore, talinolol is increasingly less absorbed along the small intestine as caused obviously by increasing expression of P-glycoprotein, that is, the second peaks after 4–6 h cannot be the results of absorption from the proximal intestine (15). Interestingly, compounds that follow the lymphatic route of absorption such as the fat-soluble vitamins A and E or drugs with extremely high lipid solubility such as halofantrine produce concentration peaks several hours after oral administration (16–18).

To evaluate whether talinolol is absorbed from the gastrointestinal tract via pathways that are associated with the uptake of lipid-soluble vitamins and that are influenced by meal, we determined the pharmacokinetics of talinolol in healthy subjects that had fasted 5 h after drug administration relative to the conditions produced by a heavy breakfast 1 h

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after oral administration, which means the time of the expected first talinolol peak. To obtain information on talinolol absorption on distal sites of the intestine, talinolol disposition was studied in fasting subjects after administration of enteric-coated capsules and rectal soft capsules. Talinolol was given in fixed combination with paracetamol to identify gastric emptying and the time of capsule disintegration because paracetamol is rapidly and completely absorbed from all parts of the gut (19). Retinol palmitate was coadministered as a second probe drug to measure absorption via the lymphatic pathway (18).

MATERIALS AND METHODS

Drug Formulations

Talinolol (100 mg), paracetamol (100 mg), and retinol palmitate (96 mg corresponding to 100,000 international units) were prepared as hard gelatin capsules, enteric-coated hard gelatin capsules, and rectal soft glycerol gelatin capsules, respectively. Enteric coating was achieved with Eudragit L 100. The enteric-coated capsules were tested using the dissolution apparatus 3 of the USP 25 at 32 dips per minute with 0.1 N hydrochloric acid and phosphate buffer pH 6.8 as test media at 37°C. The coated capsules were resistant against 0.1 N hydrochloric acid for at least 2 h and disintegrated in phosphate buffer pH 6.8 within 30 min. According to the biopharmaceutics classification system (BCS), paracetamol is of high solubility and high permeability (class I), talinolol of high solubility and low permeability (class III), and retinyl palmitate of low solubility and low permeability (class IV).

Subjects

Eight white healthy male subjects (age 21–29 years, body weight 68–86 kg, body height 180–189 cm) of good health as evidenced by history, physical examination, routine chemical and hematological screening, and assessment of 12-lead electrocardiogram were included in the study after they had given informed written consent. All had negative results in screenings for hepatitis B virus, hepatitis C virus, human immune deficiency virus, illegal drugs, and ethanol. The drug screening was performed with the Triage-8 kit (Biosite Incorporated, San Diego, CA, USA); the alcohol screening was done with the ADX-analyzer (Abbott, Wiesbaden, Germany). The subjects did not take medications and abstained from alcohol during the whole study. The study protocol had been approved by the local ethics committee.

Study Protocol

The study was performed controlled, randomized, and open according to a four-period changeover design with a wash-out period of 7 days. Randomization has been done in blocks of two mirrored Latin squares (n = 4). In each pharmacokinetic study period, a single dose of the study medication described above was administered in the morning after overnight fasting for at least 10 h. The noncoated hard gelatin capsules and the enteric-coated capsules were swallowed with 200 ml tap water (room temperature). The rectal soft capsule was pushed deep into the rectum. In the fourth treatment period, hard gelatin capsules were given 1 h prior to a continental breakfast that consisted of 2 scrambled eggs, 2 sausages, butter, 2 rolls, and herb tea. In all study periods, a standard lunch was given 5 h after the medication. After administrations of noncoated hard gelatin capsules, 5-ml blood samples were collected before and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36 h after oral administration. After enteric-coated capsules, the blood sampling times were as follows: 0, 0.5, 1.0, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, 16, 24, 36 h. Urine was completely collected for 3 days. The subjects abstained strictly from smoking, alcohol, and caffeine containing food stuffs and/or beverages for 1 day before the respective kinetic study day until the last blood sampling. The serum and urine samples were stored until the quantitative analysis at least at –20°C.

Assay of Talinolol

Talinolol was assayed with an HPLC-method with fluorimetric detection as described elsewhere (8). In brief, 0.5 ml serum was mixed with 0.1 ml saturated sodium carbonate and 0.025 ml internal standard solution (75 ng/ml *d,l*-propranolol) and extracted with 5 ml diethylether. After evaporation, the residue was dissolved in 120 μl of the mobile phase (0.025 mol/L triethylammonium phosphate buffer pH 3.0, isocratically mixed with 23% acetonitrile) of which 20 μl were injected into the HPLC (Merck-Hitachi, Darmstadt, Germany) equipped with the fluorescence detector F1050 and the following column: EcoCart 250-4 HPLC cartridge filled with LiChrospher 60 RP-select B (temperature 30°C, flow 0.8 ml/min). Peak heights of the fluorescence signals were measured at 252 nm (extinction) and 332 nm (emission) to assess talinolol concentrations with the internal standard method. The limit of detection was 0.5 ng/ml. The method was validated for serum concentrations between 5 and 1000 ng/ml. The intra-assay accuracy of the method was 0.4% to 7.7% of the nominal concentrations used for calibration (relative error) and precision was –4.6% to 4.1% of means (coefficient of variation). The following inter-assay data were obtained with quality control samples containing 25, 250, and 750 ng/ml talinolol: accuracy 5.1% to 6.6%, precision 2.4% to 4.9% of the nominal and mean quality control values, respectively. Urine was assayed for talinolol, 4-*trans*-, 3-*trans*-, and 3-*cis*-hydroxy talinolol as recently described (20). The inter-assay accuracy of talinolol was 3.0% to 7.9% of the metabolites 0.8% to 7.0%, precision values were –3.9% to 6.3% for talinolol and –7.1% to 7.8% for the metabolites.

Assay of Paracetamol

Paracetamol was assayed with the same HPLC instrument equipped with the UV/VIS detector L4250 (Merck-Hitachi, Darmstadt, Germany) and the following column: EcoCart 125-3 HPLC cartridge (Merck, Darmstadt, Germany) filled with LiChrospher 100 RP-18e. The drug was extracted from 0.5 ml serum after addition of the internal standard 7-(β-hydroxyethyl) theophylline and denaturation (acetonitril) with 3 ml acetic acid ethyl ester. The validation range was 0.1–2 μg/ml. The intra-assay accuracy and precision were 0% to 0.7% of the nominal concentrations and –3.0% to 2.8% of means, respectively. The inter-assay results were as follows: accuracy 0.1% to 3.6%, precision –3.1% to 4.2% of the nominal and mean values, respectively.

Assay of Retinyl Palmitate

The HPLC instrument was coupled to the UV-DAD detector L4500 (Merck-Hitachi, Darmstadt, Germany) and with the column LiChroCart 125-4 HPLC cartridge (Merck, Darmstadt, Germany) filled with LiChrospher 100, RP-18. The vitamin was extracted from serum with acetic acid ethyl ester. The range of validation was 0.05–6.6 μg/ml. The intra-assay accuracy and precision were 0.2% to 3.9% and –9.8% to 6.7%, respectively. The inter-assay quality was as follows: accuracy 2.2% to 7.1%, precision –17.8% to 12.1% of the nominal and mean values, respectively.

Pharmacokinetic Evaluation

C_{max}, t_{max}, and lag-time (t_{lag}) were obtained directly from the measured concentration-time curve. The double-peak of talinolol was characterized with t_{max1} and t_{max2}. Half-life ($t_{1/2}$) was estimated by log-linear approximation of the terminal data points. $AUC_{0\text{-}t}$ was assessed by the trapezoidal rule up to the last sampling time with a concentration above the limit of quantification. $AUC_{0\text{-}\infty}$ was calculated by addition of the extrapolated part after the last sampling time with a concentration above the limit of quantification to $AUC_{0\text{-}t}$ using standard techniques. The apparent total systemic clearance (CL/F) was determined from dose/$AUC_{0\text{-}\infty}$. Renal (CL_R) and metabolic clearance (CL_M) were calculated with the amount of talinolol and its metabolites, respectively, excreted into urine (A_e). Residual clearance was derived from $CL_{res} = CL/F - CL_R - CL_M$. Arithmetic means ± standard deviations (SD) are given. Sample statistics was performed with the nonparametric Wilcoxon test. For all pharmacokinetic and statistical evaluations, the SAS 8.0 program package was used (SAS Institute Inc., Cary, NC, USA).

Pharmacokinetic Model

An open three-compartment model was used to describe the serum concentrations-time profiles (Fig. 1). For all calculations, the SAAM II software (SAAM Institute Inc., Seattle, WA, USA) was used using Akaikes information criterion (AIC) as the objective function for the numerical optimization (21). In a first step, previous pharmacokinetic data with intravenous talinolol (10) were fitted in order to obtain the first-order rate constants $k_{10} = 0.020\ min^{-1}$, $k_{12} = 0.061\ min^{-1}$, $k_{21} = 0.034\ min^{-1}$, $k_{13} = 0.063\ min^{-1}$, $k_{31} = 0.0041\ min^{-1}$. Fixing these constants, the volume of distribution V_d, the lag time t_{lag}, and the absorption constants k_{a1}, k_{a2} (Fig. 1) were determined for the individual serum concentrations obtained during fasting over 5 h after administration of the capsule. Using SAAM II, the delay is modeled as a chain of compartments, specified by the lag time t_{lag} and the number of compartments N within the delay. According to previous data, an oral bioavailability f_{total} of 65% was assumed (10). The fraction of talinolol dose that is drained from the intestine via a presystemic storage pathway (f_L) was calculated as $f_L = k_{a2}/(k_{a1} + k_{a2})$.

Finally, t_{lag}(fed) and f_{total}(fed) were determined for the individual serum concentrations of the subjects after serving a breakfast. As the absorbed dose is not a fit parameter in SAAM II, V_D was taken as variable and the oral bioavialability was then calculated as $f_{total}(fed) = V_D(fasted)/V_D(fed) \times f_{total}(fasted)$. All other constants remained fixed. In all calculations, a constant lag time of 10 min was assumed for disintegration of the capsules and for gastric emptying.

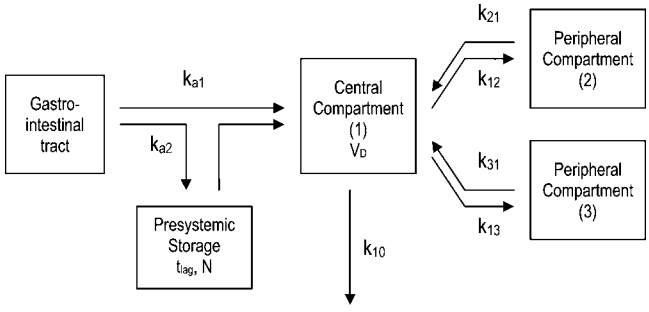

Fig. 1. Three-compartment open model with modified absorption that was used for numerical simulation of the serum concentration-time curves of talinolol after oral and rectal administration: k_{a1} is the rate constant for direct absorption into the central compartment; k_{a2} represents the rate constant for absorption into a presystemic pathway. The delay is modeled as a chain of N compartments, from which the drug is released into the central compartment after a lag time (t_{lag}); k_{12}, k_{21}, k_{13}, and k_{31} are equilibration rate constants between the central and peripheral compartments, and k_{10} is the elimination rate constant.

RESULTS

Intestinal absorption of talinolol from all galenic forms was irregular (Figs. 2A, 2C, and 2D). After administration of the fast disintegrating capsules, a distinct double-peak phenomenon of talinolol occurred in all subjects with a first maximum approximately 1 h and a second peak about 3–6 h after administration. The maximums of paracetamol appeared 15 ± 11 min before the first talinolol peak. After oral administration of enteric-coated capsules, a clear-cut double-peak phenomenon was not observed. Paracetamol reached maximum serum levels 45 ± 62 min before talinolol. After rectal administration, talinolol was also erratically and delayed absorbed and reached double-peaks, plateau phases, or slow concentration-increasing and concentration-decreasing phases. In contrary, paracetamol was more regularly absorbed from the rectum and reached clear-cut peaks after 1.75 ± 0.80 h.

Administration of talinolol in form of enteric-coated and rectal soft capsules was associated with significantly decreased relative bioavailability (AUC) and maximum serum concentrations (C_{max}) by about 50% and 80%, respectively. Talinolol given as enteric-coated capsules was also slower eliminated (Table I).

The extent of paracetamol absorption was nearly identical from all galenic forms. Due to the slower absorption of paracetamol from enteric-coated capsules and rectal soft capsules, respectively, the C_{max} values were significantly decreased by about 45% and 65%, whereas elimination half-lives were increased (Table II).

Administration of talinolol in fast disintegrating capsules followed by a standard meal after 1 h was associated with faster absorption of the drug and higher maximum serum concentrations compared to administration with meal after 5 h (Fig. 3, Table III). Instead of the first peak, there was solely a slight shoulder of the mean absorption slope. A distinct first peak occurred only in 5 subjects with t_{max} nearly identical to paracetamol (Figs. 2A and 2B). C_{max} of the second peak was significantly increased but appeared markedly earlier. Ad-

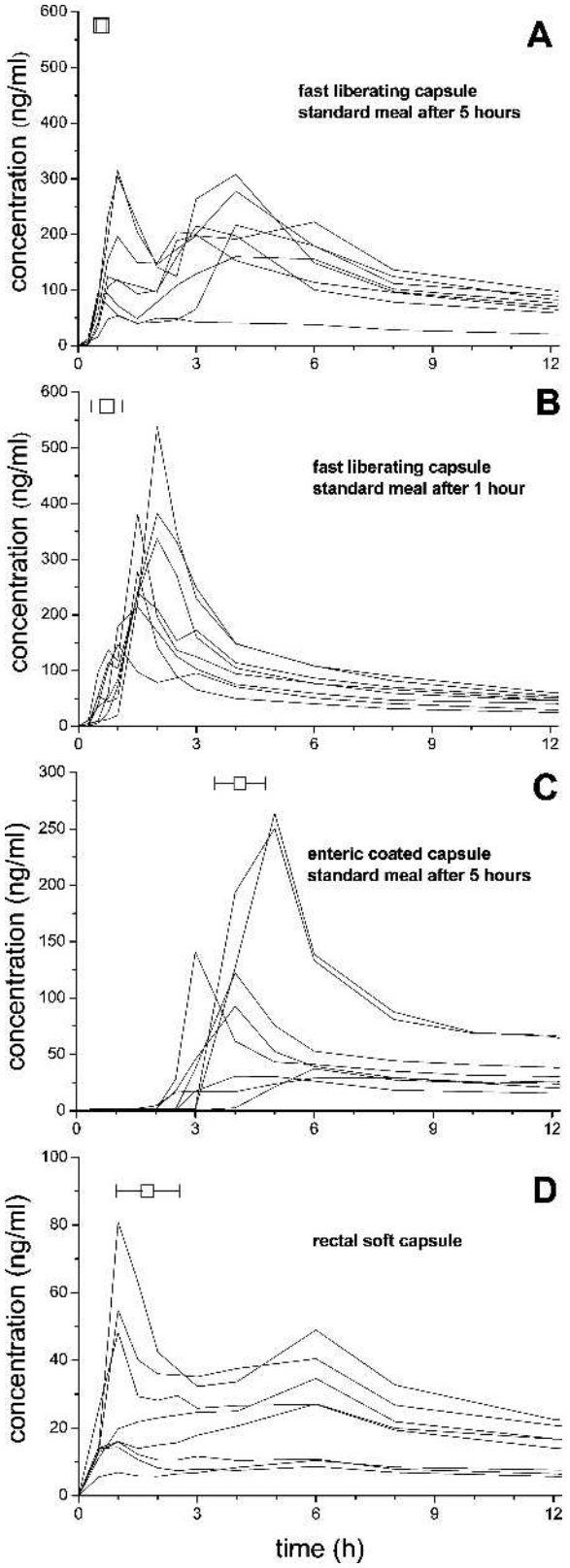

Fig. 2. Individual concentration-time profiles of talinolol in 8 healthy subjects after oral administration of 100 mg talinolol in hard capsules followed by a standard meal after 5 h (A) and after 1 h (B), respectively. The pharmacokinetic profiles of talinolol given in enteric-coated capsules are shown in (C) and after rectal soft capsules in (D). The squares with horizontal error bars indicate means ± SD of the t_{max} of paracetamol, which was given together with talinolol.

Table I. Pharmacokinetic Characteristics of Talinolol After Administration of 100 mg in Hard Capsules, Enteric-Coated Capsules, and Rectal Soft Capsules in 8 Healthy Male Subjects[a]

		Hard capsule	Enteric-coated capsule	Rectal soft capsule
$AUC_{0-\infty}$	(ng · h/ml)	2635 ± 832	1330 ± 590*	540 ± 263*
C_{max}	(ng/ml)	223 ± 75.8	121 ± 94.0	35.8 ± 24.3*
t_{lag}	(h)	—	3.31 ± 0.92	—
t_{max1}	(h)	0.84 ± 0.23	4.88 ± 1.55*	2.88 ± 2.59
t_{max2}	(h)	3.75 ± 1.16	—	—
$t_{1/2}$	(h)	12.3 ± 1.39	17.5 ± 3.18*	14.8 ± 5.15
CL/F	(ml/min)	755 ± 472	1457 ± 552*	4147 ± 2655*
CL_R	(ml/min)	179 ± 26	130 ± 45*	201 ± 121
CL_M	(ml/min)	2.94 ± 1.66	3.54 ± 1.98	10.8 ± 14.9*
CL_{res}	(ml/min)	573 ± 459	1324 ± 542*	3935 ± 2641*
A_e	(mg)	28.2 ± 9.0	10.0 ± 4.6*	6.89 ± 6.11*

[a] Data are expressed as mean ± SD. Differences were assessed by the Wilcoxon test (*$p < 0.05$, compared to hard capsules).

ministration of talinolol 1 h before meal was associated with significantly lower AUC and lower amount excreted into urine (A_e), indicating that food has reduced the extent of talinolol absorption. Renal and metabolic clearance was not changed by food.

In subjects fasting over 5 h after administration of the capsule, maximum serum concentrations of retinyl palmitate appeared after 7.3 ± 2.4 h, which means 2.9 ± 1.5 h after the second talinolol peak. After meal, the vitamin was significantly faster absorbed ($p < 0.05$) to reach maximum levels 3.5 ± 1.1 h after administration and 1 h after the second talinolol peak, respectively. Disposition of paracetamol was not influenced by subsequent meal.

The kinetic parameters found by model fit were (mean ± SD): $k_{a1} = 0.0091 \pm 0.0063\ min^{-1}$, $k_{a2} = 0.0132 \pm 0.0073\ min^{-1}$, $n = 28 \pm 18$, and the fraction representing the second peak results was $f_2 = 59 \pm 16\%$, A lower mean value for the bioavialability f_{total} was found (51 ± 16% instead of 65%) in our model calculation as well as for the lag time (59 ± 44 min instead of 171 ± 32 min) in the subjects receiving a meal 1 h after administration of the capsule. The contributions of the two absorption pathways to the plasma profiles are shown in Fig. 4. The mean AIC value for the fit of the individual serum concentrations of subjects fasting over 5 h after administration of the capsule is 4.73 ± 0.88. The respective value for the subjects after serving a breakfast is 5.14 ± 0.37.

Table II. Pharmacokinetic Characteristics of Paracetamol After Administration of 100 mg in Hard Capsules, Enteric-Coated Capsules, and Rectal Soft Capsules in 8 Healthy Male Subjects[a]

		Hard capsule	Enteric-coated capsule	Rectal soft capsule
$AUC_{0-\infty}$	(ng · h/ml)	3958 ± 764	3721 ± 803	3748 ± 757
C_{max}	(ng/ml)	1387 ± 98.4	774 ± 290*	498 ± 79.7*
t_{lag}	(h)	—	3.00 ± 0.71	—
t_{max}	(h)	0.59 ± 0.13	4.13 ± 0.64*	1.75 ± 0.80*
$t_{1/2}$	(h)	2.59 ± 0.28	2.80 ± 0.64	3.73 ± 0.62*

[a] Data are given as mean ± SD. Differences were assessed by the Wilcoxon test (*$p < 0.05$, compared to hard capsules).

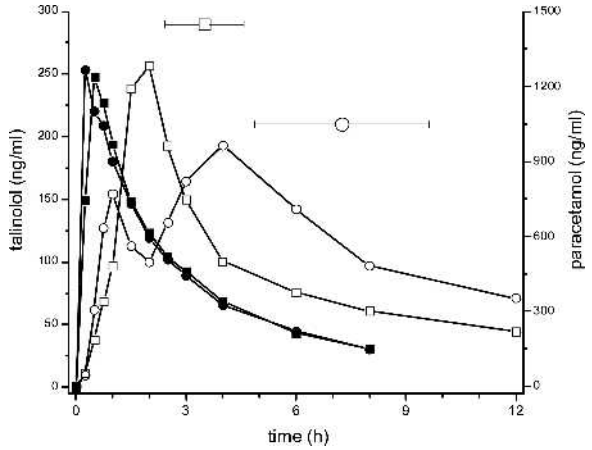

Fig. 3. Mean serum concentration-time profiles of talinolol (open symbols) and paracetamol (filled symbols) in 8 subjects fasting 10 h before and 5 h after oral administration of hard capsules (circles) and fasting 10 h before and 1 h thereafter (squares), respectively. The circles and squares with horizontal error bars indicate the respective means ± SD of the t_{max} of retinyl palmitate, which was given together with talinolol and paracetamol.

DISCUSSION

We have shown in healthy subjects that the extent and rate of talinolol absorption are dependent on the site of *in vivo* liberation and on processes associated with the uptake of food.

Paracetamol as a component of our study medication is rapidly and completely absorbed from all parts of the intestine except from the stomach therefore being a suitable probe drug to evaluate gastric emptying and the location of intestinal absorption (19,22). Accordingly, talinolol in fast-disintegrating capsules must have been taken up immediately after gastric emptying because it appears in the blood nearly coincidently with paracetamol. Nevertheless, about half of the absorbed dose attained the blood with a delay of 4–6 h as discussed below. Drugs in enteric-coated capsules are known to disintegrate predominantly in the distal jejunum or the ileum (23). This is in accordance with the long lag times of talinolol (3.3 h) and paracetamol (3.0 h) in our study. The absorption of talinolol from more distal sites of the small intestine was decreased for about 50% and from the rectum for about 80% as compared to the upper small intestine. Talinolol from rectal soft capsules was completely liberated into the rectum as concluded from adequate paracetamol absorption, which was equivalent in extent to the other formulations.

Site dependence of oral absorption seems to be a common property of the substrates of P-glycoprotein (P-gp), a multidrug transporter of the ABC-family. Several authors have measured increased expression and/or function of P-gp longitudinally along the small intestine (stomach < jejunum/ileum) (24–29). Others, however, could not verify regional differences in MDR1mRNA expression (30). Nevertheless, the substantial variability of talinolol absorption from modified release capsules is in line with our conception on regional differences in intestinal P-gp expression because talinolol is a nonmetabolized substrate of P-gp (15,31–33). It was clearly shown with a triple lumen tube perfusion technique in man that talinolol is markedly less absorbed after administration into more distal regions (95–115 cm vs. 160–235 cm behind the teeth). Interestingly, the overall profiles of the plasma concentrations curves were not changed after distal perfusion (15). Consequently, the later after oral administration a capsule containing talinolol disintegrates, the lower is the bioavailability of talinolol.

A regular pharmacokinetic finding for talinolol given as fast-disintegrating dosage forms is the double-peak phenomenon. The first peak after oral administration is plausibly explained by fast intestinal uptake into the blood as verified by nearly coincident paracetamol maximums. However, the second peak cannot be explained by site-dependent absorption. The distal small intestine from which talinolol after oral administration should have been absorbed to produce a large maximum after 4–6 h is less permeable for talinolol as explained above. This excludes an uptake via watery channels (solvent drag phenomenon), which is not counteracted by P-gp (13,34). The paracellular absorption of talinolol seems to be low and not influenced by net water absorption, similar to the structurally related atenolol (35).

Other reasons for double-peak phenomena as they are discussed in literature do also not apply for talinolol. First, enterohepatic recycling is not likely associated with irregular talinolol absorption, as biliary secretion of the drug accounts

Table III. Pharmacokinetic Characteristics of Talinolol in 8 Healthy Male Subjects After Oral Administration of 100 mg in Hard Capsules Followed by a Standard Meal After 5 Hours (F) and 1 Hour (NF), Respectively.[a]

	$AUC_{0-\infty}$ (ng × h/ml)		C_{max} (ng/ml)		t_{max1} (h)		t_{max2} (h)		$t_{1/2}$ (h)		CL_R (ml/min)		CL_M (ml/min)		CL_{res} (ml/min)		A_e (mg)	
	F	NF	F	NF	F	NF	F	NF	F	NF	F	NF	F	NF	F	NF	F	NF
I	2391	2082	199	239	0.75	1.50	3.00	3.00	11.5	12.6	190	138	3.51	1.99	503	661	27.8	17.4
II	2249	2182	215	337	1.00	0.75	3.00	2.00	10.8	12.3	173	130	0.44	3.33	568	631	23.4	17.4
III	2922	2754	217	382	1.00	—	4.00	2.00	12.9	11.9	154	192	3.74	3.37	413	410	27.6	32.3
IV	2721	1735	160	215	0.50	—	4.00	1.50	13.1	13.4	183	184	1.22	1.63	428	775	30.1	19.3
V	3330	2411	316	538	1.00	—	6.00	2.00	10.0	9.8	214	212	2.13	2.67	284	476	43.2	31.1
VI	3070	1203	308	278	1.00	0.50	4.00	1.50	12.4	14.1	174	168	3.65	7.67	365	1210	32.8	12.7
VII	3519	2060	278	381	1.00	0.75	4.00	1.50	14.1	13.2	135	104	3.08	1.33	335	704	29.2	13.0
VIII	877	1384	94	147	0.50	1.00	2.00	3.00	13.4	14.9	208	193	5.77	1.84	1686	1010	11.2	16.2
M	2635	1976*	223	315*	0.84	0.90	3.75	2.06*	12.3	12.8	179	165	2.94	2.98	573	735	28.2	19.9*
SD	832	516	76	122	0.23	0.38	1.16	0.62	1.4	1.5	26	37	1.66	2.04	459	265	9.0	7.6

[a] Data are given as mean ± SD. Differences were assessed by the Wilcoxon test (*$p < 0.05$).

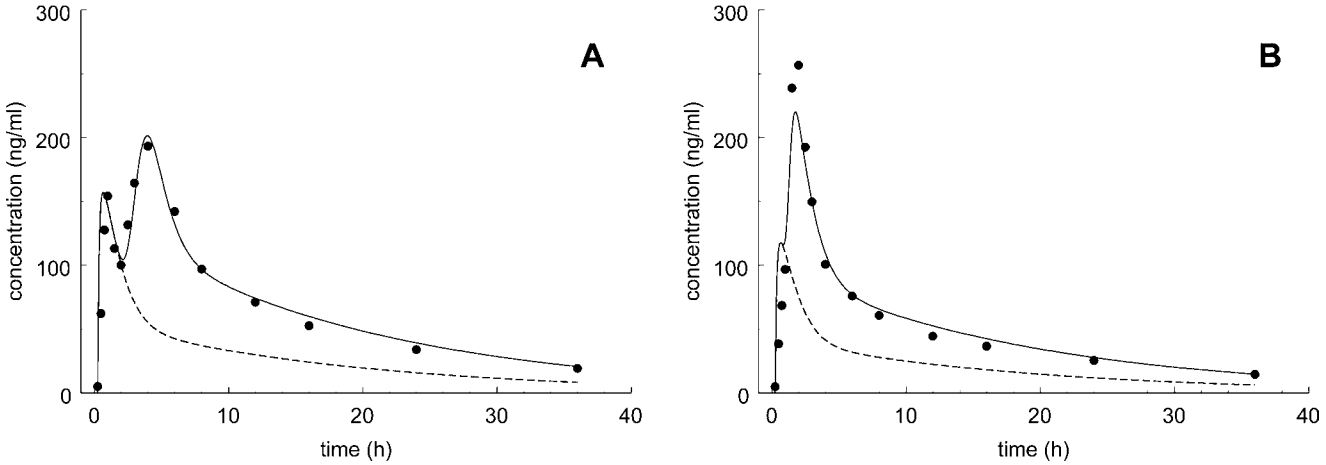

Fig. 4. Comparison of the mean serum concentrations of talinolol (full circles) measured after administration of 100 mg in hard capsules given 5 h before meal (A) and 1 h before meal (B) with the serum-concentration time curves as assessed by model fit (full line). In addition, the calculated contribution of the direct absorption pathway to the mean plasma profile is shown (dashed line).

for less than 10% of an intravenous dose, and as there were no fluctuations after administration of talinolol in enteric-coated capsules and after intravenous administration (10,14). Second, fractionated gastric emptying has been doubtlessly excluded by our results with the concomitant dosed paracetamol. Paracetamol is not a P-gp substrate; its absorption profile provides information on the kinetics of gastric emptying without being suspected to interfere with talinolol absorption.

There is ample evidence that talinolol passes the apical membrane of intestinal enterocytes at least as fast as paracetamol. This uptake is counteracted by P-gp leading to reduced availability in the jejunum/ileum and rectum. According to our observation (Fig. 4), about half of the absorbed oral dose appears in blood nearly at the same time as paracetamol or even before paracetamol. The other part obviously follows a nonmetabolic presystemic processing, leading to delayed bioavailability. After the breakfast that was served 1 h after swallowing of fast-disintegrating talinolol capsules, the late peak shifted dramatically to shorter t_{max} values and overlapped with the first peak. Residues of the latter could be identified in most subjects as a small absorption shoulder. The subsequent meal slightly decreased the total extent of talinolol absorption most likely by binding of not-absorbed talinolol (and/or re-secreted by P-gp) to food components or to bile acids as shown also for the β-adrenoreceptor blockers atenolol and pafenolol (8,36,37). Binding to bile acids is assumed to cause double-peaks in the plasma curves of pafenolol in rats. Accordingly, pafenolol forms rapidly micellar complexes with bile acids in the proximal small intestine, which terminates the initial absorption. Dissociation of these micelles in the distal ileum leads to the major second pafenolol peak in plasma (8). In presence of food, the binding to bile acids is less significant, leading to nonrestricted absorption in the jejunum. In man, the second peak disappeared when a solution of the drug was coadministered with food (8). However, we have administered talinolol in both study periods after overnight fasting. Food was eaten in our study 1 h and 5 h after (!) medication, that is, talinolol was able to form complexes with bile acids under fasting condition for at least 1 h. Furthermore, we could show with the model fits that it is possible to adjust the plasma concentrations curves using a model where only the oral bioavailability and the lag time are taken as variable and the proportion of the fractions of talinolol absorbed via the first and second pathways remain constant. This indicates that food has influenced the presystemic entero-hepatic absorption pathways of talinolol behind the apical membrane of enterocytes.

The acceleration of talinolol absorption by a fat-rich meal was associated with faster uptake of the fat-soluble vitamin A from the gut. The intestinal processing of vitamin A is closely coupled with the processing of fat by solubilization in mixed micelles, reesterification, incorporation into chylomicrons, and secretion in the lymph (38,39). Water-insoluble peptide-type molecules (e.g., cyclosporin A) and some lipophilic drugs with high triglyceride solubility (≥100 mg/ml) and high octanol/water partition coefficient ($\log p \geq 5$) are also in part absorbed via this pathway (18,40). These compounds are assumed to be transported in association with the lipid core of the lipoproteins. One example is halofantrine, which is faster absorbed after meal to reach manifold higher C_{max} compared to the fasting state (41). There may be many interactions of the non-ionized form of talinolol ($\log D = 1.1$) with the enterocyte lipid and peptide processing microdomains, which may possibly explain its absorption in association with dietary components of the meal. As recently shown, the intestine seems to be able to store alimentary fat for several hours within the jejunal tissue to release it into plasma following later stimuli as glucose ingestion (42).

The directional transport of drugs along the presystemic entero-hepatic pathway requires the presence and coordinate function of drug uptake as well as efflux transporters on the apical and basolateral membranes of the enterocytes and hepatocytes such as MDR1, MDR3, MRP1-6, and BCRP of the ATP binding cassette transporter family, OATP1A2, OATP1B1, OATP1B3, and OATP2B1 of the organic anion transporting polypeptide family, or OCT1-3 of the organic cation transporter family (43–46). There is evidence from drug interactions studies of talinolol with verapamil in mdr1a/1b –/– knockout mice and healthy subjects for the existence of uptake transporters for talinolol that may overshadow the influence of P-gp on talinolol absorption (47,48). Candidates are the polyspecific transporters of the OCT family, OATP2B1, and OATP1B1. OCT2 mediates in the kidneys the uptake of β-adrenoceptor antagonists across the proximal

tubule (49,50). OATP2B1 binds with low specificity many compounds with diverse chemical structure. OATP1B1 seems to be the major uptake transporter of rifampicin and statins (44,51–53). The complex interplay between intestinal uptake and kick-back processes along the apical/luminal surface, the transit throughout the highly compartmented enterocyte followed by secretion along the basolateral membrane, as well as the processes involved in hepatic uptake and secretion may lead to irregularities in plasma concentration curves such as shoulders of multiple peaks. Consequently, noncoordinate influence as caused by nutrients or transporter modulating drugs may lead to irregularities in extent and rate of talinolol absorption. Interestingly, induction of duodenal P-gp by rifampicin, carbamazepine, or thyroxine decreased the bioavailability of talinolol and/or increased its elimination rate. The double-peak phenomenon, however, remained conserved (54–56). On the other hand, comedication of the nonspecific P-gp modulators erythromycin and verapamil resulted in increased (after erythromycin) or, surprisingly, decreased (after verapamil) extent of talinolol absorption. The second peak, however, was abolished in favor of a higher first peak (47,57).

CONCLUSIONS

The double-peak phenomenon of talinolol likely results from processing via a presystemic storage compartment within or behind the intestinal absorption barrier.

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