Bioavailability of Three Commercial Sustained-Release Tablets of Quinidine in Maintenance Therapy

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Abstract □ The bioavailability of three quinidine formulations was estimated during a dosing interval at steady state following their administration in 12 selected patients in accordance with a Latin-square 3 × 3. Each subject received the three dosage forms as two tablets every 12 hr for 6 days. Blood and urine samples were taken on the 7th day during the regular 12-hr dosing interval. Unchanged quinidine was determined by a reported spectrofluorometric procedure. The total fluorescence of plasma quinidine and metabolites also was monitored. The data obtained indicate that one dosage form gave a high peak level followed by a fall in the concentration. The two other forms presented a relatively lower peak followed by a plateau and then a decline. The differences between the dose-corrected values of $C_{p,max}$ were statistically significant. Secondary effects were observed particularly with one dosage form and could be related to the high $C_{p,max}$ value and/or the high percentage of quinidine liberated rapidly in the GI tract. Blood and urinary data indicated an equivalent degree of absorption. The dissolution behavior of the formulations and their absorption data suggest that there is a correlation between the quantity dissolved at 30 min and $C_{p,max}$.

Keyphrases □ Quinidine—pharmacokinetics and bioavailability of three dosage forms compared, humans □ Bioavailability—quinidine, three dosage forms compared, humans □ Pharmacokinetics—quinidine, three dosage forms compared, humans □ Antiarrhythmic agents—quinidine, pharmacokinetics and bioavailability of three dosage forms compared, humans

Quinidine is the most widely used oral antiarrhythmic in the prophylaxis and treatment of cardiac arrhythmias (1). There is a correlation between serum drug concentration and antiarrhythmic and toxic effects (2–4). The therapeutic drug level of unchanged quinidine and hydroquinidine is 0.8–2.5 mg/liter of plasma (5). To maintain a sufficiently steady therapeutic plasma level with quinidine sulfate tablets USP, this dosage form must be administered at relatively frequent intervals because of rapid drug absorption and elimination.

Sustained-release dosage forms offer the possibility of smoother blood level–time profiles with longer intervals between doses. The dissolution rate of some quinidine sustained-release tablets and its implication in bioavailability and therapeutic treatment were studied previously (6). The present study compared the bioavailability of three commercial dosage forms, considered as slow-release formulations, by measuring the plasma drug level and the degree of drug excretion during a regular dosing interval of a maintenance treatment.

EXPERIMENTAL

Subjects—Twelve patients[1], seven men and five women, who had received quinidine treatment for at least 6 months, were randomized into three groups of a Latin-square 3 × 3. These patients ranged in age from 28 to 65 years (mean of 45), in weight from 49.2 to 101.5 kg (mean of 75), and in height from 1.54 to 1.87 m (mean of 1.71). There was no evidence of hepatic, renal, or hematopoietic disease from urinalysis, complete blood count, and determination of serum levels of creatinine, bilirubin, alkaline phosphatase, glutamic-pyruvic transaminase, and glutamic-oxaloacetic transaminase. No patient exhibited evidence of congestive heart failure or GI disease from his or her history and physical examination. Before starting the study, the patients did not receive enzymatic drug inducers for 1 month and drugs likely to interfere with the analysis for 1 week.

Drug Administration—During three consecutive 7-day periods, the subjects received each of the three dosage forms: Tablet A[2] (250 mg of quinidine bisulfate, equivalent to 165.8 mg of quinidine base), Tablet B[3] (325 mg of quinidine gluconate, equivalent to 202.5 mg of quinidine base), and Tablet C[4] (325 mg of quinidine gluconate, equivalent to 202.5 mg of quinidine base). Two tablets of each dosage form were ingested every 12 hr for 6 days.

Each patient received a card to record the time at which each dose was taken. These cards indicated that the difference between the recorded and the prescribed times of ingestion was less than 20 min during the first 5 days and 10 min during the 6th day. On the 7th day, the morning dose of the dosage form that had been taken for 6 days was administered with 200 ml of water after an overnight fast of at least 10 hr. During the first 3 hr after drug administration, the subjects were not allowed to eat or to lie down but were asked to drink water at a rate approximately 70 ml/hr. Each subject received a standard meal after this period.

Specimen Collection and Assay—Blood sampling (6 ml) for quinidine determination was conducted with an indwelling catheter at 0.0, 0.5, 1.0, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 10.0, and 12.0 hr following the morning dose of the 7th day. Patency of the catheter was maintained with a slow infusion of 5% dextrose solution. Blood specimens were collected in heparinized tubes.

The tubes were subsequently centrifuged, and the plasma was removed and frozen until assayed by the specific spectrofluorometric procedure[5] of Armand and Badinand (5, 7). Although the specificity of this method is limited, it was sufficiently sensitive, accurate, and precise for the measurement of concentrations as low as 0.1 μg/ml (5). Total quinidine-derived fluorescence also was monitored by the protein precipitation method of Brodie and Udenfriend (8). For each urine void, the volume was determined and an aliquot was frozen until just prior to drug analysis by the method of Armand and Badinand (5, 7). Quinidine levels are reported in terms of quinidine base.

Hydroquinidine Determination—Since the two procedures used for quinidine also measure hydroquinidine (5), the percentage of hydroquinidine as a contaminant was determined in each product. The high-speed liquid chromatographic procedure[6] reported by Pound and Sears (9) was used.

Data Analysis—The bioavailability of the three dosage forms was determined by comparing the: (*a*) plasma concentrations at each sampling time, (*b*) dose-corrected[7] peak plasma concentration, (*c*) time to attain the peak plasma concentration, (*d*) area under the plasma concentration–time curve (*AUC*) during the dosing interval [corrected for the dose and normalized to (mg/liter)(hr/m^2)], and (*e*) percentage of the dose of quinidine excreted unchanged during the dosing interval. The efficacy of the three dosage forms was evaluated by comparing the duration of the different minimum effective plasma concentrations that could be required for different patients.

The *AUC* was estimated by means of the trapezoidal rule. Statistical significance was determined by analysis of variance (ANOVA) (10) after verifying the homogeneity of variances by the Bartlett test (11). Com-

[1] Written informed consent was obtained after discussing with each subject the inconveniences and hazards.

[2] Biquin, lot AM405, Astra Chemicals Ltd., Mississauga, Ontario, Canada.
[3] Quinate, lot 04TG, Rougier Inc., Chambly, Quebec, Canada.
[4] Quinaglute, lot R51002, Cooper Laboratories, Wayne, N.J.
[5] Aminco-Bowman spectrofluorometer, American Instrument Co., Silver Spring, Md.
[6] Model 8500 high-pressure liquid chromatograph, Varian Associates, Palo Alto, Calif.
[7] Parameters of Tablet A corrected for the dose are multiplied by 202.5/165.8.

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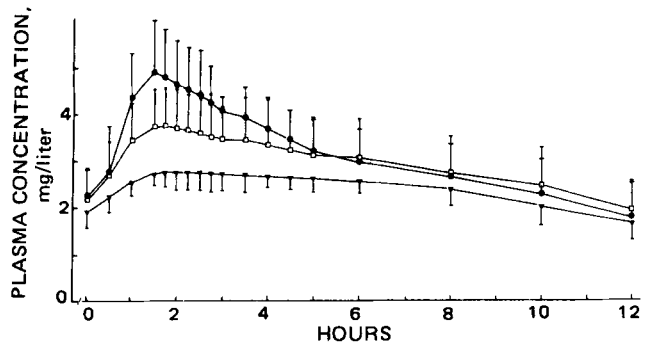

Figure 1—*Mean plasma concentration of intact drug for three different quinidine products during a 12-hr dosing interval of a maintenance treatment. Key: ●, Tablet B; □, Tablet C; and ▼, Tablet A. The vertical bar represents the standard deviation.*

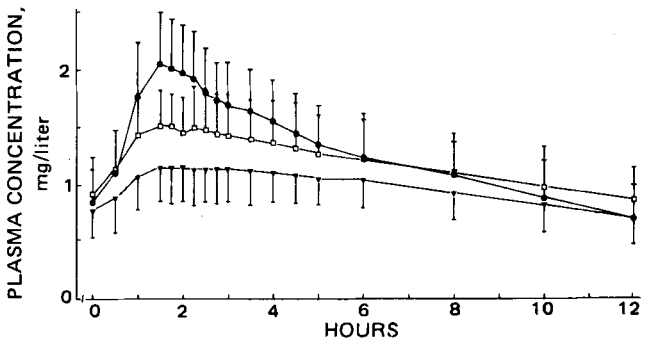

Figure 2—*Mean plasma concentration of total drug for three different quinidine products during a 12-hr dosing interval of a maintenance treatment. Key: ●, Tablet B; □, Tablet C; and ▼, Tablet A. The vertical bar represents the standard deviation.*

puter programs written in Fortran were used for the estimation of the *AUC* and the realization of the analysis of variance and the Bartlett test. Differences between individual treatments were determined by the Newman–Keuls multiple-range test (12).

Dissolution Test—Four dosage units of each product were subjected to a dissolution test using a USP dissolution assembly equipped with a continuous fluid exchange system to change the pH of the medium progressively. The method was described previously (13).

RESULTS

Figures 1 and 2 illustrate the mean plasma concentration–time profile of the corresponding unchanged and total drug during the 12-hr dosing interval for the three products tested. Although initial and final plasma concentrations for each product were similar, the values of the maximum plasma concentration varied considerably for a given method. The variation of plasma concentration at each sampling time was determined by the analysis of variance; Table I summarizes this analysis at time zero.

The statistical analysis at different blood sampling times indicated that a significant difference ($p < 0.05$) can be observed only with the intersubject and treatment factors. No significant difference ($p > 0.05$) was observed for the group, period, and period–treatment factors. For the intersubject factor of the plasma concentration of unchanged quinidine at different times after drug administration, a significant difference was observed at 0, 0.5, 4.0, 4.5, 5.0, 6.0, 8.0, 10.0, and 12.0 hr. The treatment factor of plasma concentration of intact quinidine was statistically significant from 0.5 to 5.0 hr following drug administration. For this latter period, the rank order of plasma concentration was Tablets A, C, and B. The Newman–Keuls *a posteriori* test indicated that there was a significant difference between each plasma concentration obtained with the three products between 1.0 and 4.5 hr. At 0.5 and 5.0 hr, the difference between plasma concentrations observed with Tablets B and C was not statistically significant. The statistical analysis of total quinidine plasma concentrations at different times yielded very similar results.

Some pharmacokinetic parameters estimated from plasma and urine data of unchanged quinidine are given in Table II. The analysis of variance on the parameters listed in this table showed that there was a significant difference for the intersubject factor with $C_{p,\min}$, Cl_p, *AUC*, $t_{0.8}$, $t_{1.0}$, and $t_{1.2}$ and for the treatment factor with some parameters. No significant difference was observed for the group, period, and period–treatment factors. The unifactorial analysis of variance (14) used for % D_u and Cl_r parameters, because of some missing urine samples, allows the variability evaluation of the treatment factor only.

The statistical analysis of the values of the dose-corrected *AUC* and the percentage of the dose excreted unchanged in the urine, % D_u, derived from each patient revealed that there was no significant difference in the degree of quinidine absorption from these dosage forms. A statistical difference was not observed for the time required to attain the peak concentration, t_{max}, of the individual plasma concentration–time curves exhibited with the three treatments. However, a statistical difference between the three products was evidenced for the dose-corrected maximum plasma concentration, $C_{p,max}$, obtained from the individual plasma concentration–time curves.

A statistical difference also was found for the three treatments in their difference between the dose-corrected maximum and minimum plasma concentrations measured at the end of the dosing interval, ΔC_p, in each patient. For the three products tested, the difference between the duration of a minimum effective plasma concentration of 1.0 or 1.2 mg/liter, but not of 0.8 mg/liter, was significant.

The dissolution behavior of the three formulations and their absorption data (Fig. 3) suggest that there is a correlation between the quantity dissolved at 30 min and the observed maximum plasma drug concentration.

DISCUSSION

With a consideration of the quinidine dose administered and the assumption of linear pharmacokinetics, the degree of drug absorption from the three products was similar. However, between 1 and 4.5 hr, a statistically significant difference was observed for plasma concentrations obtained with Tablets C and B, which were administered at the same dose. The highest level was obtained with Tablet B. The dose-corrected $C_{p,max}$ value of Tablet B was significantly different from that of A and C. Furthermore, the dose-corrected ΔC_p values demonstrated that Tablets A and C presented similar fluctuation in blood levels and that this fluctuation was less pronounced than for B. Consequently, the statistical analysis of the data and the plasma level–time profiles shown in Fig. 2 indicated that Tablet B did not present the sustained-release properties observed by Goldberg and Chakrabarti (15), who reported plasma levels based on the total fluorescence of quinidine and metabolites. Slow-release characteristics were not observed. Results of this in-

Table I—Analysis of Variance of the Plasma Concentrations of Unchanged Quinidine at Time Zero [a]

Source of Variation	Sum of Squares	Degrees of Freedom	Mean of Squares	*F*	*p*
Between subjects	2.050	11	0.186	6.41	<0.01
Groups	0.383	2	0.191	1.03	>0.25
Subjects within groups	1.667	9	0.185	—	—
Within subjects	0.698	24	0.029	0.16	>0.25
Periods	0.009	2	0.005	0.15	>0.25
Treatments	0.131	2	0.065	2.11	>0.10
Period–treatment	0.001	2	0.0004	0.01	>0.25
Error	0.557	18	0.031	—	—
Total	2.748	35	—	—	—

[a] The test of Bartlett (11) for the homogeneity of variances indicated that the value of the calculated χ-square is smaller than the critical χ-square value for $p = 0.05$.

Table II—Pharmacokinetic Parameters Estimated from Plasma Levels and Urinary Excretion of Intact Drug

Parameter[a]	$\bar{X}$[b] A	$\bar{X}$[b] B	$\bar{X}$[b] C	ANOVA F	ANOVA p	N.K.[c]
$C_{p,max}$, mg/liter	1.46 (0.36)	2.14 (0.41)	1.59 (0.34)	29.13	<0.01	A C B
$C_{p,min}$, mg/liter	0.84 (0.27)	0.69 (0.30)	0.84 (0.28)	3.12	>0.05	—
ΔC_p, mg/liter	0.62 (0.16)	1.46 (0.37)	0.75 (0.22)	51.66	<0.01	A C B
AUC, (mg/liter)(hr/m^2)	7.75 (2.38)	8.22 (2.31)	7.86 (2.86)	0.39	>0.05	—
% D_u	19.1 (4.0)	16.4[d] (6.5)	16.1[e] (2.9)	1.34[f]	>0.05	—
t_{max}, hr	1.81 (0.40)	1.65 (0.36)	1.62 (0.46)	0.75	>0.05	—
$t_{0.8}$, hr	8.35 (3.65)	9.72 2.73)	9.69 (3.12)	1.39	>0.05	—
$t_{1.0}$, hr	5.02 (4.59)	7.93 (3.41)	7.6 (4.3)[e]	4.75	<0.05	A C B
$t_{1.2}$, hr	2.29 (3.89)	6.05 (3.73)	5.38 (4.98)	5.97	<0.05	A C B
Cl_r, ml/min/m^2	50.75 (12.14)	44.96[d] (24.28)	46.47[e] (11.06)	0.36[f]	>0.05	—
Cl_p, ml/min/m^2	274.56 (82.83)	260.84 (93.28)	274.48 (72.33)	0.35	>0.05	—

[a] The abbreviations used for parameters are: $C_{p,max}$ = maximum drug plasma concentration corrected for the dose; $C_{p,min}$ = minimum drug plasma concentration corrected for the dose; $\Delta C_p = C_{p,max} - C_{p,min}$; AUC = area under the plasma concentration–time curve corrected for the dose; % D_u = percentage of dose excreted; t_{max} = time to attain peak plasma concentration; $t_{0.8}$, $t_{1.0}$, and $t_{1.2}$ = period of time where the plasma level of unchanged drug is greater than 0.8, 1.0, and 1.2 mg/liter, respectively; Cl_r = renal clearance estimated from the amount of unchanged quinidine base excreted in the urine during the dosing interval divided by the AUC; and Cl_p = plasma clearance estimated from the equation: Cl_p = (fraction of dose absorbed)(dose of quinidine base)/(AUC) in assuming that the absorption is complete. [b] Arithmetic mean value. The value in parenthesis is the standard deviation. [c] Newman–Keuls multiple-range test. Drug products underlined by the same line are not significantly different ($p > 0.05$). [d] Mean of 11 subjects. [e] Mean of 10 subjects. [f] Unifactorial analysis of variance.

vestigation and previous dissolution data (6) suggest that Tablet B must have been reformulated.

The effects of quinidine are related to high plasma levels and/or high local concentrations in the GI tract (2–4). In this study, Tablet B presented a high dissolution rate and a high maximum plasma concentration (Fig. 3). Therefore, a higher frequency of side effects after its administration would be expected. In this investigation, two patients complained of vertigo, visual disturbances, and cold sweat for 1–2 hr after ingestion of Tablet B during the 1-week treatment. Five subjects reported having some diarrhea: four with Tablet B (one patient for the whole duration of the treatment and three patients for several days during the 6-day loading portion) and one with Tablet C (for many days during the treatment). Patients demonstrating side effects after receiving Tablet B had a mean maximum plasma concentration of 2.0 mg/liter. This value did not differ significantly from the $C_{p,max}$ observed with patients receiving this product and not showing side effects. Therefore, this result was apparently due to the fact that toxic as well as therapeutic responses to quinidine are determined by individual patient sensitivity (16).

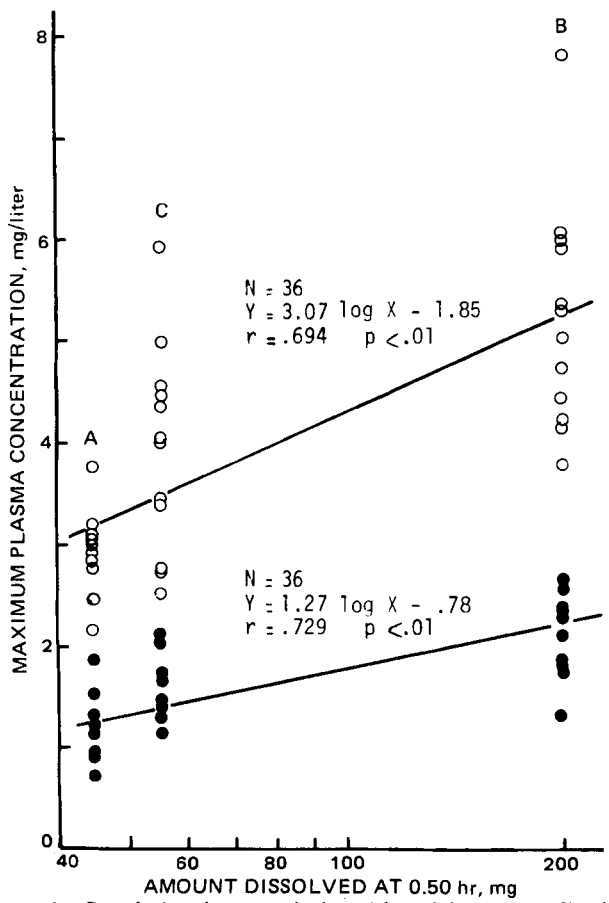

Figure 3—*Correlations between the logarithm of the amount dissolved at 0.5 hr and the maximum plasma concentration. Key:* ●, *intact quinidine; and* O, *total quinidine.*

In view of the sensitivity factor in a quinidine treatment (16), it is important to realize that the minimum effective concentration required for obtaining the desired pharmacological effect will vary from one patient to another. The efficacy of the three products can thus be evaluated by determining their ability to produce and to maintain a given minimum plasma concentration during the dosing intervals of a maintenance treatment. In patients requiring a plasma level of 0.8 mg of unchanged drug/liter, the statistical analysis of the data (Table II) indicated that the three products tested would give the same protection. Patients requiring a level of 1.0 or 1.2 mg/liter would get a relatively good prophylaxis with Tablets B and C. Consequently, the dose required to give these levels with Tablet A should be increased.

The biological half-life was estimated from the data of Tablet B by regression analysis on the linear terminal portion of the relation between ln C_p and time. The biological half-life was calculated using:

$$t_{1/2} = -0.693/\text{slope} \qquad \text{(Eq. 1)}$$

When using the plasma concentration of unchanged quinidine, the mean half-life for all subjects was 7.16 hr with a standard deviation of 2.29 and a range of 3.44–12.15 hr. This range corresponds closely to the results reported previously (17, 18). The mean half-life calculated from the plasma concentration of total quinidine gave nearly the same value (7.46 hr with a standard deviation of 2.36). The similarity between these two values demonstrates that the rate constants for overall elimination of metabolites must be greater than the overall elimination (metabolism and renal excretion of unchanged drug) rate constant of quinidine (19).

The mean renal clearance value given in Table II is very close to that reported previously (18, 20). The mean plasma clearance value is similar to the one reported by Mahon *et al.* (20) but higher than the one obtained by Ueda *et al.* (18) after infusion. This difference would result mainly

from first-pass hepatic drug removal when quinidine is administered orally (21).

The two procedures used in this work measure the total fluorescence of either the unchanged quinidine and hydroquinidine or the two unchanged alkaloids and their metabolites (5). As a result, the contamination by hydroquinidine would be expected to produce a certain error in the evaluation of quinidine pharmacokinetic parameters. However, the corresponding percentages of hydroquinidine in Tablets A, B, and C were only 8.23, 4.33, and 6.71, respectively. Furthermore, a study on the pharmacokinetics of quinidine and hydroquinidine by Ueda *et al.* (22) indicated that the differences in the distribution and elimination characteristics of the two alkaloids are not significant. In view of these facts, the bias introduced in the value of quinidine pharmacokinetic parameters estimated in this work (Table II) appears to be negligible.

Several parameters measured in this study demonstrated significant intersubject variability. This observation is in agreement with previously published works and demonstrates the need to individualize the dosage regimens of this drug (18). Drug monitoring with a given dosage form is usually based on the range of plasma concentrations known to produce the desired therapeutic response in most patients. However, better drug monitoring could be obtained if the adjustment of the dose is also based on therapeutic and toxic effects observed in individual patients.

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Ditheophylline Succinate: Transfer of Theophylline across Everted Rat Intestinal Sacs

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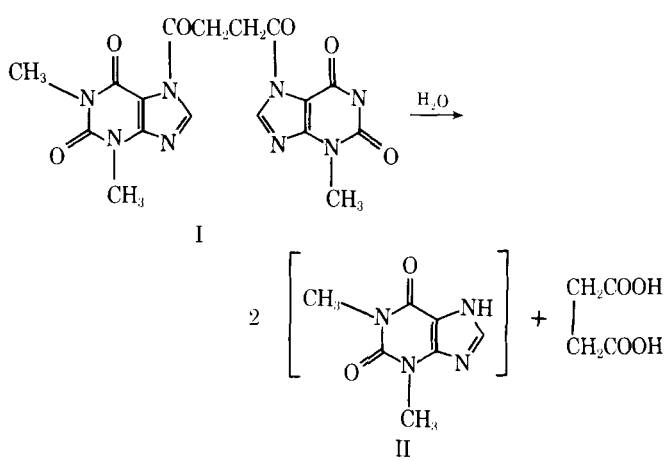
Abstract □ The cumulative theophylline transfer rate across 10-cm everted rat intestinal sacs incubated at 37° in pH 7.4 Krebs phosphate buffer was determined. A suspension of ditheophylline succinate (a potential prodrug of theophylline) and a solution of theophylline at equimolar concentration were evaluated to determine the magnitude of the difference between the cumulative theophylline transfer rates from the two preparations. A linear concentration dependency for the rate across the intestinal wall was evidenced. The theophylline formation rate from ditheophylline succinate suspended in pH 7.4 Krebs buffer at 37° followed apparent zero-order kinetics. The observed difference (fourfold) between the cumulative transfer rates estimated for the theophylline solution and the ditheophylline succinate suspension was attributed to the prevailing theophylline concentration in the mucosal solutions. The biopharmaceutical implications of these observations are discussed.

Keyphrases □ Ditheophylline succinate—theophylline transfer rate across everted rat intestinal sacs □ Theophylline—transfer rate across everted rat intestinal sacs □ Transfer rate—theophylline from solution and ditheophylline succinate suspension across everted rat intestinal sacs □ Prodrugs—ditheophylline succinate, theophylline transfer rate across everted rat intestinal sacs □ Relaxants, smooth muscle—theophylline, transfer rate across everted rat intestinal sacs

7,7′-Ditheophylline succinate[1] (I) is a potential theophylline prodrug. In the presence of moisture or water, it hydrolyzes rapidly to yield two molecules of theophylline (II) and one molecule of succinic acid[2] (Scheme I).



Scheme I

The aqueous solubility of I is less than 0.1 mg/ml; however, the dissolved material undergoes ultrafast hydrolysis

[1] SC-30163.

[2] H. K. Lee and H. Lambert, Internal Report DVR7611023, Searle Laboratories, Chicago, IL 60680.

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