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COMMUNICATION

Studies of Erythromycin Maltobionate, a New Derivative of Erythromycin

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ABSTRACT

Erythromycin maltobionate, a new water-soluble derivative of erythromycin, was prepared, and its physicochemical and biological properties were evaluated. The derivative has considerable solubility in organic solvents. Its partition coefficient data in different organic solvent-water systems indicate it is possibly well distributed in various tissues in vivo. Antimicrobial potency in vitro of the derivative is 589 μg/mg, and its antimicrobial spectrum is comparable to that of the parent antibiotic. The LD_{50} *value of the new derivative in mice intraperitoneally is 244.7 mg/kg. Results of this and the previous investigation of pharmacokinetics and protein binding indicate that the new derivative erythromycin maltobionate has a potential for possible clinical application.*

INTRODUCTION

Erythromycin is a macrolide antibiotic that is bitter in taste and slightly soluble in water (2 mg/ml). Its pK_a value is 8.9, and thus it is ionized throughout the entire gastrointestinal (GI) tract and absorbed adequately from the upper portion of the GI tract, except from the stomach (1,2), but the absorption is irregular (3). Erythromycin is unstable under the acidic conditions of the stomach or in pH values less than 4.0 (4). Large intersubject variability in serum concentration occurs after oral administration even under standardized conditions (5,6), whereas intersubject variability in pharmacokinetic parameters after intravenous erythromycin is small (7), indicating that the majority of intersubject variability is due to erratic absorption and differences in absolute bioavailability. Due to this reason, the drug was listed by the American Pharmacy Association Academy of Pharmaceutical Sciences as having serious bioavailability and/or quality assurance problems.

In attempts to avoid problems of solubility, taste, and degradation in gastric juice and to optimize absorption,

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a large number of formulations and derivatives (viz. salts, esters, ester salts, and ester prodrug) (8–23) have been prepared from time to time since its introduction in 1952 (24). The authors also attempted from time to time to prepare derivatives of erythromycin (21–23) with better potency and bioavailability, as well as less toxicity. Erythromycin maltobionate is one such new salt of erythromycin prepared by the authors. The pharmacokinetics in the animal model and in vitro protein binding of the salt reported by Basu, Manna, and Goswami (25) are encouraging, and hence the new salt erythromycin maltobionate was subjected to further evaluation in the present study.

MATERIALS AND METHODS

Preparation of the Salt

Erythromycin maltobionate was prepared by the method of Dutta and Basu (25,26) by reacting erythromycin base (Abbott Laboratories, North Chicago, IL) with free maltobionic acid liberated from lithium maltobionate by passing the latter through a cation exchange resin (Amberlite IR-120). The salt was recovered by lyophilization.

Physicochemical Properties

Melting point, microanalytical composition, solubility, optical rotation, partition coefficient, pH of aqueous solution, thin-layer chromatography, and infrared spectroscopic investigations were carried out.

The solubilities of erythromycin maltobionate in H_2O, 0.1N HCl, phosphate buffer pH 7.4, and nine organic solvents were determined by the method of Marsh and Weiss (26). Erythromycin base was used as a reference standard.

Optical rotation of a 1% (w/v) solution of erythromycin maltobionate in 90% (v/v) ethanol was measured at 29°C in a Perkin-Elmer polarimeter (Model No. 241), and the specific rotation was computed.

The partition coefficients of the new antibiotic salt in two different solvent systems were determined.

The pH of a 1% aqueous solution of the compound was determined in an expanded-scale pH meter (Ec model No. pH 821 A); from the pH value, the pK_a value was computed theoretically from the equation pK_a = 14 − pk_b (27).

The infrared spectrum of the compound was recorded in a Perkin-Elmer infrared spectrophotometer (237B).

Biological Properties

The biological properties studied for the antibiotic compound include in vitro antimicrobial potency, in vitro antimicrobial spectrum, and acute toxicity.

In vitro potency was determined following the method of Grove and Randall (28) using *Sarcina lutea* ATCC 9341 as the test organism.

The in vitro antimicrobial spectrum was determined by the twofold agar dilution test (29) using brain heart infusion agar (Difco) medium. Erythromycin base USP (952 μg/mg) was used as a control during the antimicrobial spectrum study.

The acute toxicity test of Litchfield and Wilcoxon (30) was followed to determine the LD_{50} value. Swiss strain male albino mice (20–25 mg), fasted for 18 hrs with water ad libitum, were injected intraperitoneally with a solution of the antibiotic compound in a propylene glycol–water mixture (1:1). One vehicle control group was used at each dosage level.

RESULTS AND DISCUSSION

Physicochemical Properties

The new derivative, erythromycin maltobionate, is a white, amorphous, fluffy powder. Its melting point is between 140°C and 145°C. Specific rotation, computed from the optical rotation of a 1% (w/v) solution in etha-

Table 1

Solubility Data of Erythromycin Maltobionate and Erythromycin Base at Room Temperature (33°C ± 1°C)

	Solubility (mg/ml)	
Solvent	Erythromycin Maltobionate	Erythromycin Base
Water	>20	2.1
Acetone	12.2	>20
Methanol	>20	>20
Ethanol	>20	>20
Chloroform	7.75	>20
Ethyl acetate	4.8	>20
Benzene	6.0	>20
Propylene glycol	>20	>20
Cyclohexanol	>20	>20
1:4 Dioxan	6.0	>20
Phosphate buffer, pH 7.4	>20	>1.8
0.1 N HCl	>20	>20

Table 2

pH, pK_a, and Partition Coefficient of Erythromycin Maltobionate

pH of 1% Aqueous Solution	pK_a	Partition Coefficient	
		Chloroform : Water	Cyclohexanol : Water
6.75	5.3	0.15	0.3

nol (90% v/v), was −52° for erythromycin maltobionate, whereas it was −69°C for erythromycin base.

The microanalytical composition of erythromycin maltobionate (7.93% hydrogen, 53.7% carbon, and 1.25% nitrogen) was found to corroborate well with the theoretical values.

The solubility data of erythromycin maltobionate (Table 1) indicates that, in contrast to the parent antibiotic, the salt is more soluble in water and other polar solvents and less soluble in nonpolar solvents. The solubility decreases with decreasing polarity of the solvent system.

The pH, pK_a, and partition coefficient of the erythromycin salt are given in Table 2. The salt's partitioning is better in cyclohexanol than in chloroform.

Thin-layer chromatographic investigation of the prepared salt in various solvent systems ensured homogeneity of the prepared salt. The Rf values are furnished in Table 3.

The infrared absorption spectra of erythromycin base and erythromycin maltobionate showed major absorption bands at or around 3400 cm^{-1}, 1725 cm^{-1}, and 1590 cm^{-1}. The absorption band at or around 3400 cm^{-1} indicates the presence of an intact, many-membered lactone ring of erythromycin in erythromycin maltobionate. The absorption band at or around 1590 cm^{-1} confirms the formation of the quaternary ammonium salt of erythromycin of the type given in Fig. 1.

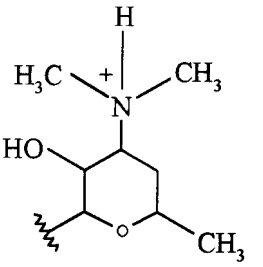

Figure 1. Quaternary ammonium salt of erythromycin.

Biological Properties

The in vitro potency of erythromycin maltobionate was found to be 589 μg/mg. The in vitro antimicrobial spectrum of erythromycin maltobionate (Table 4) was found to be very close to that of erythromycin base.

The LD_{50} value of erythromycin maltobionate was found to be 244.7 μg/mg, which is satisfactory for safe clinical use.

CONCLUSION

The results of the present investigation show that the new derivative, erythromycin maltobionate, is more po-

Table 3

Rf Values of the Erythromycin Maltobionate and Erythromycin Base in Different Solvent Systems Using Silica Gel G Plates

Solvent System	Erythromycin Maltobionate	Erythromycin Base
Methanol : ethyl Acetate : water 1 : 1 : 2	0.27	0.23
Chloroform : methanol : acetic acid 90 : 9 : 1	0.05	0.12
Chloroform : methanol 1 : 1	0.43	0.54
Chloroform : methanol : ethyl acetate 1 : 1 : 2	0.23	0.40

Table 4

In Vitro Antimicrobial Spectra of Erythromycin Maltobionate and Erythromycin Base

Organism	Minimum Inhibitory Concentration[a] (mcg/ml)	
	Erythromycin A Base	Erythromycin Maltobionate
Salmonella typhi 59	30	40
Staphylococcus aureus 8530	<0.15	0.20
Staphylococcus aureus 178	0.15	0.30
Staphylococcus aureus 180	>100	>100
Staphylococcus aureus 10541	0.05	0.1
Shigella flexneri 3189	12	20
Shigella sonnei 56	17	25
Bacillus pumilus 8241	0.15	0.3
Bacillus subtilis ATCC 8241	50	60
Bacillus subtilis ATCC 6633	0.15	0.30
Pseudomonas aeruginosa B-27	>100	>100
Proteus mirabilis 75	>100	>100
Klebsiella pneumoniae 77	>100	>100
Escherichia coli K12	55–60	70
Vibrio cholerae 564	17	30

[a] Values shown are base equivalents of the salt.

tent than most of the existing derivatives of erythromycin. Its solubility increases with increasing polarity of the solvent system and vice versa. It partitions between aqueous and organic phases, indicating that it is likely to be absorbed and transported well in vivo, and it is safe enough from the clinical point of view.

In a previous study on pharmacokinetics in an animal model and protein binding in vitro, Basu et al. (25) reported that the erythromycin maltobionate has a short elimination half-life (83 min) and large overall apparent volume of distribution (343%) and is highly bound to plasma protein (88.5%). The elimination half-life is comparable to the elimination half-lives of erythromycin and its existing derivatives (ca. 1.5 hr). The value of overall apparent volume of distribution corroborates well with the protein-binding data. The large overall apparent volume of distribution indicates that erythromycin maltobionate is bound more extensively to extravascular sites than to the plasma protein (31). The reports of Basu et al.'s previous study (25) corroborate well with physicochemical properties found in the present study and are consistent with earlier reports (32–35) that erythromycin penetrates tissues extensively. The increased water solubility of the new derivative compared to the parent antibiotic will make it suitable for its possible use in an aqueous solution form.

From the data of the present study and the previous study, it may be concluded that erythromycin maltobionate is likely to have a good potential for clinical use, and further necessary investigations to that effect may be undertaken.

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