Comparison of Observed and Predicted Bioavailability of Nortriptyline in Humans following Oral Administration

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Abstract □ The first-pass equation based on the dose, hepatic blood flow, and total area under the plasma level–time curve after oral administration was used retrospectively to predict the bioavailability of nortriptyline after oral administration of 1 mg/kg-single oral doses to monozygotic and dizygotic twin pairs. The predicted values of bioavailability ranged from 45 to 85%, consistent with experimentally derived estimates of nortriptyline availability.

Keyphrases □ Nortriptyline bioavailability in humans—predicted by first-pass equation, compared retrospectively to oral administration in twin pairs □ Hepatic metabolism, first-pass effect—comparison of observed and predicted nortriptyline bioavailability in humans

The availability of nortriptyline was assessed in three healthy subjects by comparing the areas under the plasma concentration *versus* time curves after oral and intramuscular administration of identical doses of the hydrochloride salt (1). The observed availability in these subjects ranged between 56 and 70% (mean of 64%). Complete GI absorption of nortriptyline is suggested by the fact that the recovery of the main urinary metabolite, 10-hydroxynortriptyline, was essentially the same following both routes of administration. The results suggest that, in humans, a significant fraction of the absorbed drug is lost to the systemic circulation during the first pass through the liver (1).

DISCUSSION

The following equation was developed to predict the degree to which a drug that is completely absorbed and eliminated exclusively by hepatoportal metabolism is subject to first-pass metabolism (2):

$$f = \frac{\text{flow rate}}{\text{flow rate} + \left(\text{dose} \Big/ \int_0^\infty C_0\, dt\right)} \qquad \text{(Eq. 1)}$$

where f is the fraction of the orally administered dose that actually reaches the systemic circulation (*i.e.*, the predicted availability), flow rate is the hepatic blood flow rate, and $\int_0^\infty C_0\, dt$ is the total area under the plasma concentration *versus* time curve after oral administration.

The value of Eq. 1 lies in the fact that it requires only concentration–time data after oral administration and a reasonable estimate of hepatic blood flow. This equation has been applied with reasonable success to studies in humans with propranolol (2) as well as with propoxyphene and alprenolol (3). Nortriptyline, like propranolol, propoxyphene, and alprenolol, is virtually completely metabolized in humans (4).

Extensive pharmacokinetic studies (5) in twin pairs receiving 1 mg/kg-single oral doses of nortriptyline hydrochloride afforded the opportunity to evaluate retrospectively the applicability of Eq. 1 as a predictor of nortriptyline availability in humans.

Table I—Apparent Clearance and Predicted Availability Values after Oral Administration of 1 mg/kg-Single Oral Doses of Nortriptyline Hydrochloride to Five Monozygotic Twin Pairs

Subject	Apparent Clearance[a], liters/min	Predicted Availability (f)
15	1.42	0.52
16	1.72	0.47
25	0.80	0.66
26	0.82	0.65
39	0.90	0.63
40	0.85	0.64
47	1.04	0.60
89	0.96	0.61
78	0.46	0.77
88	0.45	0.77
Mean ± 1 *SD*	0.94 ± 0.39	0.63 ± 0.09

[a] Calculated from Ref. 5.

EXPERIMENTAL

The term $(\text{dose}/\int_0^\infty C_0\, dt)$ in Eq. 1 is equivalent to the "apparent clearance" reported in Ref. 5 in terms of (liters per kilogram) (hour) and reexpressed in Tables I and II in terms of liters per minute. The predicted availability (f) of nortriptyline was calculated for each subject by substituting the individual apparent clearance and a mean blood flow rate of 1.53 liters/min (6) in Eq. 1. These values are also reported in Tables I and II.

RESULTS

As expected, the intrapair variation with respect to f averaged

Table II—Apparent Clearance and Predicted Availability Values after Oral Administration of 1 mg/kg-Single Oral Doses of Nortriptyline Hydrochloride to Six Dizygotic Twin Pairs

Subject	Apparent Clearance[a], liters/min	Predicted Availability (f)
9	1.09	0.58
10	0.94	0.62
27	0.66	0.70
28	0.39	0.80
31	1.90	0.45
32	1.22	0.56
68	0.63	0.71
81	0.78	0.66
74	0.64	0.71
80	0.27	0.85
92	0.88	0.63
94	0.48	0.76
Mean ± 1 *SD*	0.82 ± 0.44	0.67 ± 0.11

[a] Calculated from Ref. 5.

only 3% in the monozygotic twins; in fact, it was virtually negligible in four of five pairs. Intrapair variation with respect to predicted availability in the dizygotic twins averaged about 14%. The mean predicted availability was essentially identical in both groups. The predicted availabilities in all subjects ranged between 45 and 85%, which is consistent with the range of 56–70% observed in a study with three subjects (1). The mean predicted availability of 65% was in perfect agreement with the previously observed mean (1).

This retrospective study provides greater confidence in the reliability of Eq. 1 as a predictor of average bioavailability for drugs undergoing first-pass metabolism.

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Effects of Acids and Bases on Salicylic Acid–Cetrimide Systems

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Abstract □ The effects of acids and bases on the viscosity of salicylic acid–cetrimide systems were investigated. A viscosity reduction was produced by the addition of acids and was independent of the degree of saturation of the cetrimide solution with salicylic acid. The incorporation of base followed by that of acid increased and decreased the viscosity, respectively. This viscosity behavior was demonstrated in undersaturated systems and was not governed by the relative amounts of base or acid used. In oversaturated systems, only a lowering of viscosity was observed.

Keyphrases □ Salicylic acid–cetrimide systems—effects of various acids and bases on viscosity □ Cetrimide–salicylic acid systems—effects of various acids and bases on viscosity □ Viscosity—salicylic acid–cetrimide systems, effects of various acids and bases

Since solutions of alkaline sodium salts have been shown to effect different changes in the viscosity of salicylic acid–cetrimide systems (1), a study of the reaction of the viscosity of the systems to acid additives was considered desirable. It was also the purpose of this investigation to determine whether the viscosity change arising from the addition of either acid or base is retained when these additives are added alternately to the same system. This approach is an attempt to test the sensitivity of the viscous property to these additives. A literature survey did not reveal information on this particular area of research.

EXPERIMENTAL

Recrystallized salicylic acid, mp 158–159°, and cetrimide[1] BP were the same as those described earlier (2). The acids were citric acid[2], tartaric acid[3], phosphoric acid[4], acetic acid[5], lactic acid[6], 1 *N* hydrochloric acid[2], and dilute hydrochloric acid BP. The alkalies were 1 *N* sodium hydroxide[3] and 1 *N* potassium hydroxide[3]. These additives were selected because they are representative of relatively weak acids, strong acids, and alkalies and are likely to be included in suspension formulation studies in which salicylic acid–cetrimide systems are involved.

The viscosity was measured at 25° as reported previously (2) and the pH[7] was determined.

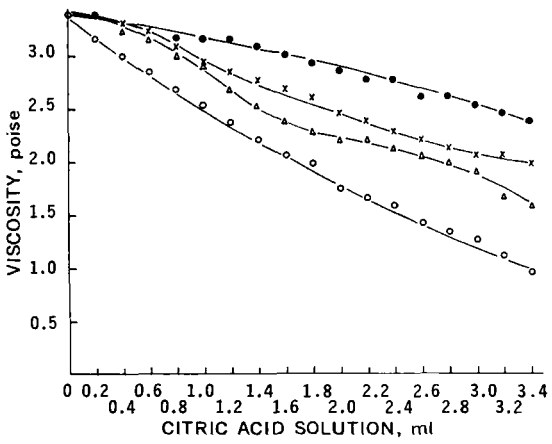

Figure 1—*Decrease in viscosity on addition of citric acid solutions of different concentrations to systems (50 g) containing 5% cetrimide and 1.4% salicylic acid at 25°. Key (citric acid, % w/v): ●, 1; ×, 4; △, 6; and ○, 10. Shear rate is 78.56 sec⁻¹.*

[1] Glovers Chemicals Ltd., Leeds 12, England.

[2] May and Baker, Dagenham, England.
[3] E. Merck, Darmstadt, Germany.
[4] Hopkin and Williams Ltd., England.
[5] British Drug Houses, Ltd., England.
[6] Larporte Industries Ltd., Ilford, Essex, England.
[7] Beckman pH expandometer, Fullerton, CA 92634