monia and extracted with diethyl ether. After drying over anhydrous magnesium sulfate, the ethereal lincomycin solution was treated with a nearly saturated solution of cyclohexylsulfamic acid (42 mg., 0.231 mmole) in methyl ethyl ketone. Instant crystallization occurred during the addition. The crystals were collected, washed with diethyl ether, dried over P_2O_5, and found to melt at 149–151° (Kofler).

Anal.—Calcd. for $C_{18}H_{34}N_2O_6S \cdot C_6H_{13}NO_3S \cdot 2H_2O$: C, 46.36; H, 7.62; N, 6.76; S, 10.31. Found: C, 46.74; H, 8.14; N, 7.45; S, 10.49.

IR spectra (Fig. 1) of the lincomycin cyclamate dihydrate showed a broad band centered at 3400 cm.$^{-1}$ for ν_{O-H} from the water of hydration as well as from other OH groups within the lincomycin molecule itself and strong bands at 1165 and 1035 cm.$^{-1}$ for asymmetric and symmetric $\nu_{S=O}$ of the sulfonic acid moiety in the ionic form characterized by Detoni and Hadzi (4). These features are also consistent with $\nu_{O=H}$ at 3412 cm.$^{-1}$ and $\nu_{S=O}$ at 1168 and 1060 cm.$^{-1}$ found for calcium cyclamate dihydrate.

An attempt was made to prepare the anhydrous lincomycin cyclamate salt by subjecting the dihydrate to a pumping vacuum (0.1 mm. Hg) while heating the salt at 100° for 2–3 hr. No dehydration could be detected by comparison of IR spectral features. While these conditions have usually been satisfactory for dehydrating a wide range of salts (5), thermal gravimetric analysis (TGA) later showed no significant weight loss (2% up to 175°, probably due to surface moisture) by the material below 230°. An upper temperature limit is imposed by melting of the salt at 150°. We were also concerned about possible thermal degradation of the cyclamate salt, having observed a remarkably easy degradation of the hydrochloride salt (6) during evaporation of an aqueous ethanolic solution (pH 2) at 50° and 15 mm. Hg in a rotary evaporator. Differential thermal analysis (DTA) indicated the cyclamate salt to be much more stable than the hydrochloride and showed the following features: a small broad endothermic peak at 157° with no weight change (possibly a softening reaction) and large exothermic reactions accompanied by weight loss at 239, 323, and 506°. The sample was totally volatilized in air at 600°.

In view of these observations and our considerable difficulty in preparing lincomycin cyclamate, we conclude that the reported interference to absorption of lincomycin hydrochloride by common cyclamates does not involve a simple metathetic reaction. Since the next most likely cause of interference could arise from association of cyclamate anions with lincomycin cations in aqueous media, thermoelectric vapor phase osmometry (7, 8) was employed over the largest possible concentration range (Figs. 2 and 3) in an attempt to detect evidence of aggregation. In the absence of discontinuities in the curves of Figs. 2 and 3, it follows that no association of cyclamate with lincomycin ions occurs even in solutions slightly supersaturated with respect to lincomycin cyclamate (*e.g.*, 0.134 *M*, Fig. 2, and 0.133 *M*, Fig. 3). Other possibilities, therefore, apart from these simple physical phenomena must be considered to explain the apparent interference of common cyclamates to lincomycin therapy.

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G. A. Neville
J. C. Ethier
Research Laboratories
Food and Drug Directorate
Department of National Health and Welfare
Ottawa, Ontario, Canada

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Comparative Systemic Availability of Acetaminophen when Administered Orally as Such and as Acetophenetidin

Keyphrases ☐ Acetaminophen systemic availability—acetaminophen, acetophenetidin administration ☐ Systemic availability, correlation—acetaminophen-precursor administration

Sir:

Phenolic drugs are metabolized to glucuronides and sulfates in man and animals (1). The systemic availability of some of these drugs upon oral administration may be decreased appreciably by biotransformation in the gastrointestinal mucosa and during the "first pass" through the liver (2–4). Acetaminophen (4′-hydroxyacetanilide) is a widely used analgesic and antipyretic agent which is eliminated mainly by glucuronide and sulfate formation (5). The related compound acetophenetidin (4′-ethoxyacetanilide) is largely converted in the body to acetaminophen (6). If acetaminophen is metabolized appreciably during absorption, its systemic availability should be relatively increased by administering its precursor, acetophenetidin, which has its phenolic group blocked and therefore protected from conjugation in the gut wall.

Prescott *et al.* (7) determined acetaminophen concentrations in the plasma upon oral administration of 1.8 g. acetaminophen or acetophenetidin to groups of normal subjects. They also determined the total urinary

Table I—Systemic Availability of Acetaminophen when Administered Orally as Such and as Acetophenetidin[a]

Administered Drug	Number of Subjects	A, mcg./ml./hr. Uncorrected	A, mcg./ml./hr. Corrected for Difference in "Dose"[b]	$A \cdot \beta$, mcg./ml.	$A \cdot \beta$ Ratio, Acetaminophen to Acetophenetidin
Acetaminophen, Trial I	8	102	—	34.8	1.04
Acetophenetidin, Trial I	9	65.0	85.0	33.5	
Acetaminophen, Trial II	8	80.4	—	31.5	1.06
Acetophenetidin, Trial II	7	53.4	69.9	29.7	

[a] Based on mean data from *Reference 7*. [b] A, from acetophenetidin trials multiplied by 1.19 (ratio of molecular weights, acetophenetidin: acetaminophen) and by 1.1 (ratio of urinary recovery of acetaminophen and metabolites from acetaminophen and acetophenetidin).

excretion of acetaminophen and its conjugates. These data permit the determination of areas under the plasma concentration *versus* time curve, acetaminophen disposition-rate constant, and total amount of acetaminophen derived from acetophenetidin.

The amount of free acetaminophen entering the systemic circulation (D) can be calculated from the area under the plasma concentration curve (A), the apparent volume of distribution (V), and the disposition-rate constant for acetaminophen (β), according to the following relationship (8):

$$D = AV\beta \qquad \text{(Eq. 1)}^1$$

If the value of V is not known, one can determine D/V:

$$D/V = A\beta \qquad \text{(Eq. 2)}$$

Assuming that the average apparent volume of distribution did not differ appreciably in the two groups of subjects, the calculations indicate that the systemic availability of acetaminophen when administered as such is essentially the same as when administered in the form of its precursor acetophenetidin (Table I). This suggests that the extent of inactivation of acetaminophen during absorption from the gastrointestinal tract is minor under the experimental conditions.

[1] Equation 1 applies to all systems in which elimination is by apparent first-order kinetics from the central compartment [W. J. Westlake, *J. Pharm. Sci.*, **59**, 722(1970)].

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GERHARD LEVY

Department of Pharmaceutics
School of Pharmacy
State University of New York at Buffalo
Buffalo, NY 14214

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