Mutual Independence of Release Rates of Steroids from a Topical Vehicle. Implications for Potentially Optimal Formulations

Sir:

We wish to present *in vitro* experimental confirmation of a concept advanced by one of us (T. H.) that release of active ingredients from a topical vehicle should be independent of, and uninfluenced by, the presence of a second noninteracting component. Furthermore, the rates of release should be independent of the nature of the vehicle and dependent only on the thermodynamic activity of the individual drugs. This activity would be fixed by the activity of the pure solid phase if present in excess. Thus, inclusion of two active agents could permit lower total dosages, fewer side effects, and more rapid or efficient utilization of costly active ingredients.

Single corticosteroids and combinations of these agents were incorporated into a gelled isopropyl myristate vehicle, and the amount of steroid released was measured as a function of time. Our *in vitro* data fully confirm the hypothesis that each agent is released at a rate independent of the second ingredient. This has been found to hold true for combinations of dexamethasone and prednisolone as well as for combinations of dexamethasone with betamethasone.

The steroid or steroid mixture was incorporated into the gelled isopropyl myristate by levigation. The steroid-containing gels then were filled into a 15-cm. diameter Petri dish until the gel was flush with the surface of the dish. To prevent the dish from floating during the release rate studies, a thin brass weight was placed in the dish prior to adding the gel. The entire mass then was transferred to a Pyrex crystallizing dish 9 cm. high and 17 cm. in diameter. Four hundred milliliters of distilled water was added cautiously and the supernatant liquid agitated gently after placing the entire apparatus in a 37° water bath. Samples were withdrawn for analysis at 1, 2, 4, 6, 8, and 24 hr. All samples were analyzed spectrophotometrically for steroid content.

As shown in Fig. 1, the total steroid released from a combination of 0.1% each of dexamethasone and prednisolone is exactly the sum of the individual release rates. The theoretical line was obtained simply by adding the amount of steroid released from 0.1% of each steroid alone. Similar good agreement between the hypothesized additivity of release is shown in Fig. 2 for a combination of 0.05% each of dexamethasone and betamethasone.

It seems particularly significant that the total amount of steroid released from a combination of 0.05% each of dexamethasone and beta-

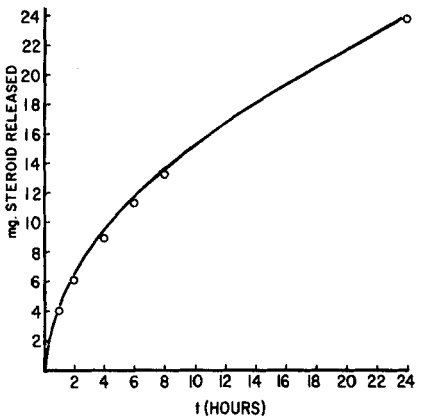

Fig. 1.—Total steroid released from 0.1% each of dexamethasone and prednisolone combined. Key: ————, theoretical sum of individual steroids; O, experimentally determined release of combination.

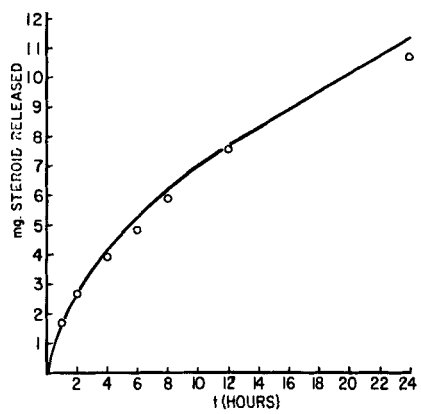

Fig. 2.—Total steroid released from 0.05% each of dexamethasone and betamethasone combined. Key: ————, theoretical sum of individual runs; O, experimentally determined release of combination.

methasone was found, at each time interval, to exceed the amount of steroid released from either 0.1% of dexamethasone or betamethasone alone. It would appear that this principle could be extended to more than two drugs and that the rate of release could be extended indefinitely until the drug mixture forms a solid solution.

Obviously only *in vivo* trials can determine if the *in vitro* advantages carry over, but the data presented do indicate that such trials merit serious consideration.

ARNOLD D. MARCUS
ROBERT E DEMPSKI
TAKERU HIGUCHI
JOSEPH D. DEMARCO

Merck Sharp and Dohme Research Laboratories
West Point, Pa.

University of Wisconsin
Madison

Received November 23, 1964.
Accepted for publication December 30, 1964.

Salicylurate Formation—Demonstration of Michaelis-Menten Kinetics in Man

Sir:

A detailed study of the pharmacokinetics of salicylate elimination in man has established, among other findings, that the formation of salicyluric acid from salicylic acid reaches a maximal rate when the body content of salicylate exceeds about 2 mmoles (approximately 300 mg. salicylic acid) in the normal human adult (1). It was found also that the renal excretion of salicylurate after administration of salicylate is rate limited by the rate of formation of salicylurate from salicylate and glycine (1). These characteristics of salicylate elimination made it possible to determine rates of salicylurate formation as a function of body salicylate content over an appreciable range.

Suitable doses of aspirin were administered orally to test subjects, total urine was collected at frequent and known intervals, and aliquots of urine were analyzed for salicylurate and total salicylate as described previously (1). The results of these experiments are describable by Michaelis-Menten kinetics (2) and yield satisfactory Lineweaver-Burk plots (3). Representative examples of the experimental results are shown in Fig. 1; the data points for subject *1* (male, 22 years old) were obtained in the period of 16 to 24 hr. after administration of 1.5 Gm. aspirin, while the data points for subject *2* (male, 36 years old) represent the period of 15 to 27 hr. after oral administration of 2.0 Gm. aspirin. The theoretical maximal velocity of salicylurate formation obtained from the Lineweaver-Burk plots is about twice as high as the maximal rate found experimentally (about 400 μm. per hour). This appears to be due to a depression by salicylate (when in sufficiently high concentration) of the glycine conjugative system, as has been observed previously with tissue slice preparations from the dog, rat, and rabbit (4).

The present findings are considered to be of unusual interest since they represent (*a*) a case of zero-order metabolism of a drug administered in usual therapeutic doses,[1] and (*b*) a demonstration of Michaelis-Menten kinetics (with respect to the metabolism of a drug) by means of data obtained from experiments with intact humans (rather than from experiments with tissue slices, cell fractions, or purified enzymes). Apparently, similar observations in humans have so far been made only with ethanol (5).

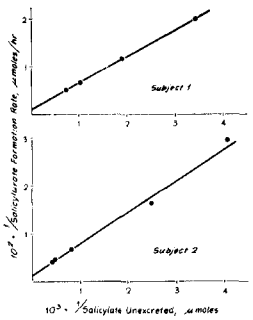

Fig. 1.—Plot of the reciprocal of salicylurate formation rate *vs.* the reciprocal of the amount of salicylate in the body.

(1) Levy, G., unpublished data.
(2) Michaelis, L., and Menten, M. L., *Biochem. Z.*, **49**, 333 (1913).
(3) Lineweaver, H., and Burk, D., *J. Am. Chem. Soc.*, **56**, 658(1934).
(4) Little, J. M., Angell, E. A., and Morgan, A. M., *Arch. Intern. Pharmacodyn.*, **111**, 259(1957).
(5) Lundquist, F., and Wolthers, H., *Acta Pharmacol. Toxicol.*, **14**, 265(1958).

GERHARD LEVY

Biopharmaceutics Laboratory
School of Pharmacy
State University of New York at Buffalo

Received December 8, 1964.
Accepted for publication January 6, 1965.
This investigation was supported in part by grant G-64-UB-1 from the United Health Foundation of Western New York.

[1] Salicylate elimination occurs mainly by salicylurate formation, ester and ether glucuronide formation, and renal excretion of unchanged drug. Zero-order kinetics have only been observed with respect to the first of these processes; the other processes are usually describable by first-order kinetics (1).