the method is convenient and sensitive for the estimation of norepinephrine. The preparation lasts for 1–3 hr if the assay is commenced soon after mounting.

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Estimation of Hepatic First-Pass Effect of Acetaminophen in Humans after Oral Administration

Keyphrases □ Acetaminophen—estimation of hepatic first-pass effect, oral administration, humans □ Metabolism—acetaminophen, estimation of hepatic first-pass effect, oral administration, humans □ First-pass effect, hepatic—acetaminophen, estimation, oral administration, humans

To the Editor:

Acetaminophen is one of the most frequently used analgesics and antipyretics today. It is primarily metabolized in humans after oral administration. In one study, only about 3–4% of the dose was recovered in urine as intact compound after dosing (1). Recently, Cohen *et al.* (2) reported that its availability to the systemic circulation after intraperitoneal administration to rats was only 34% of that after intravenous administration, indicating an extensive hepatic first-pass metabolic effect. This finding prompted them to speculate (2) that a marked variation in peak acetaminophen plasma concentrations in humans with different stomach emptying rates (3) might be caused to a varying degree by the hepatic first-pass effect.

The purpose of this communication is to estimate theoretically the extent of the hepatic first-pass effect of acetaminophen in humans, using an equation derived recently (4, 5). The following assumptions were made in the derivation: (*a*) the metabolism takes place only in the liver; (*b*) the excretion of intact drug occurs only from the kidney and/or lung; (*c*) the liver, kidneys, and lungs are part of the central compartment; (*d*) the elimination and distribution processes between the central and other peripheral compartments are all first-order processes; and (*e*) the administered drug is all absorbed after oral or intraperitoneal administration.

The fraction of the dose metabolized during the first passage to liver, f_m, can be estimated by the following equation:

$$f_m = \frac{(F_m)(\text{dose})}{\text{dose} + (HFR)(AUC)} \qquad \text{(Eq. 1)}$$

where F_m = fraction of the administered dose metabolized at infinite time, HFR = hepatic blood flow rate, and AUC = total area under blood concentration *versus* time curve in infinite time.

A search and evaluation of past studies related to acetaminophen oral absorption in humans revealed that some work reported by McGilveray *et al.* (1) was suitable for this pharmacokinetic prediction analysis. That article reported the acetaminophen blood level data up to 6 hr after oral administration of 1 g of the drug dissolved in 200 ml of water to 10 normal subjects 1.5 hr after a light breakfast. Based on the urinary excretion data and the solution dosage form administered, one could reasonably assume that all of the dose was completely absorbed (1, 6, 7).

An AUC of 5626 (min) (μg/ml) was obtained by the summation of the area from 0 to 6 hr calculated by the trapezoidal rule and of the area from 6 hr to infinity calculated by the extrapolation method (5, 7). An average biological half-life of 3.26 hr (1) was used in the calculation for the extrapolated area. This half-life is similar to (7), but different than (8), the values from studies reported by other workers, indicating the possibility of intersubject variation. The F_m was assumed to be 0.96. By substituting a value of 1500 ml/min for HFR (4, 5) and other appropriate data into Eq. 1, one obtains an f_m value of 0.102. This value is obviously much lower than those observed (f_m = 0.66) and predicted (f_m = 0.60) for rats (2).

These results indicate that there is a marked interspecies variation in the extent of the first-pass effect. Although absorption of several drugs from intraperitoneal administration has been shown to occur predominantly *via* the portal circulation in dogs and rats (9), this has not been proven for acetaminophen.

The f_m value estimated by Eq. 1 generally represents a maximum value. If the hepatic metabolic process deviates from pseudo first order as the absorption rate of drug increases (based on Michaelis–Menten enzyme kinetics), the observed f_m value would be lower than that predicted by Eq. 1. In other words, the maximum fraction of the orally administered acetaminophen dose metabolized in the liver during the first pass is only about 0.10, and the effect of the

absorption rate on the extent of the first-pass effect should be clinically insignificant.

This contention is also supported by a study that showed that although food could significantly reduce the absorption rate and peak blood levels of acetaminophen in humans, it had no significant effect on total bioavailability, as indicated by similar areas under blood concentration curves of acetaminophen (10). From this finding, it is also reasonable to suggest that differences in the contribution of the first-pass effect for rectally and orally administered acetaminophen would not be of clinical significance.

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BOOKS

REVIEWS

Drug Metabolism Reviews, Vol. 2. Edited by F. J. DICARLO. Dekker, New York, NY 10016, 1974. 308 pp. 16 × 24 cm. Price $25.50.

Drug Metabolism Reviews is presently published as an annual volume in two issues. The publisher also reissues it as a single hardbound volume. Hopefully, this removes the need for errata.

Because it originates from a periodical, this book has no master theme except that, paradoxically, while its existence cannot necessarily prove the existence of drug metabolism as a discipline its contents will help operationally define the nature and extent of the discipline; it is a series of monographs of specific interest. The value of such a collection of reviews can really be estimated only by an individual who needs the facts and/or theories presented in a review or who needs an entry into the literature of a research area. There is, then, a very definite place for such a book as *Drug Metabolism Reviews;* it does a good job of meeting a well-defined need. It should not be expected to be of uniformly general interest.

Some monographs are of more general interest in that they cover general drug metabolic interrelationships or mechanisms illustrated by specific examples. There are four such reviews. Comparative Aspects of Mixed Function Oxidation by Lung and Liver of Rabbits (Gram), Intermediates in Drug Metabolism Reactions (Hucker), The Influence of Stereochemical Factors on Drug Disposition (Jenner and Testa), and The Nature and Distribution of Enzymes Catalyzing the Conjugation of Glutathione with Foreign Compounds (Chasseaud).

Other monographs deal with a specific compound or compounds of a given structural or therapeutic class. There are four such in this book; The Role of Ascorbic Acid in Drug Metabolism (Zannoni and Lynch), The Metabolism of Biological Alkylating Agents (Jones), Metabolism and Biochemical Pharmacology of Guanethidine and Related Compounds (Lukas), and Recent Views on the Mechanisms of Nitrate Ester Metabolism (Litchfield). There is one review on methodology, another important area; Automated Assay of Drugs in Body Fluids (Rhodes and Hone). Each of these reviews contains at least some degree of critical evaluation of the subject matter. The editor is to be congratulated for avoiding the presentation of a series of annotated bibliographies.

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Clinical Pharmacokinetics: A Symposium. Edited by GERHARD LEVY. American Pharmaceutical Association, Academy of Pharmaceutical Sciences, 2215 Constitution Ave., N.W., Washington, DC 20037, 1974. 180 pp. 15 × 23 cm. Price $5.00.

Clinical pharmacokinetics represents the embodiment of sophisticated advances in Clinical Pharmacology and Pharmacokinetics with the promise of rational drug therapy. It allows for quantitative precision in defining and evaluating a predictable and reproducible clinical response. The book "Clinical Pharmacokinetics: A Symposium" provides a compilation of manuscripts by acknowledged investigators in the field of pharmacokinetics. Although it contains a potpourri of contributions rather than being a tightly organized and coordinated series of presentations, it represents a useful overview and starting point in the organization and implementation of a clinical pharmacokinetics program.

The chapters dealing with the organization of a clinical pharmacokinetics laboratory are somewhat personalized. However, contrasting these two chapters emphasizes the point that the organization and design of such a laboratory depends, to a large extent, on the interactions established with the other disciplines of the clinical team. Defining this orientation must precede the development of the laboratory. This can vary from an analytically oriented laboratory which monitors drug levels as a service function, to the research laboratory where pharmacokinetic and pharmacodynamic interrelationships are defined.

One essential aspect of a clinical pharmacokinetics program which is not sufficiently emphasized in the book is the develop-