Trichloroethyl Carbonate: Influence of Particle Size on Oral Toxicity in Mice

Sir:

The authors have reported that the particle size of 4-acetamidophenyl 2,2,2-trichloroethyl carbonate (ATC) has a great influence on its oral toxicity in mice and on the peak blood levels of acetaminophen it produces in mice and humans (1). These studies confirmed that, with prodrugs such as ATC which are relatively insoluble in water, particle size can have a marked influence on the onset and peak magnitude of the biological effects elicited.

Trichloroethyl carbonate,[1] a prodrug of trichloroethanol (2), has been reported to have an aqueous solubility of about 4 mcg./ml. (3). Therefore, it was expected that particle size would affect its oral toxicity in mice in a manner similar to that observed for ATC. The present study was carried out to determine the extent to which particle size influences the oral LD_{50} of trichloroethyl carbonate in mice.

means of a glass-Teflon tissue homogenizer; and coarse particle, prepared by sieving the drug and suspending the U. S. No. 140 to U. S. No. 170 mesh particles in a 0.5% dispersion of gum tragacanth in water. Photomicrographs of the suspensions are shown in Fig. 1.

The LD_{50}'s of the three particle sizes of trichloroethyl carbonate were determined orally in male Carworth Farms mice, weighing 14–21 Gm., in a manner similar to that used for ATC (1). The results (Table I) show that the three particle sizes of trichloroethyl carbonate had significantly different toxicities at the 95% confidence limit.

These results are very similar to those obtained with ATC. In the ATC study (1), the drug, in various particle sizes, was given orally to mice

TABLE I—ORAL LD_{50}'S WITH 95% CONFIDENCE LIMITS[a] FOR FINE, REGULAR, AND COARSE PARTICLE TRICHLOROETHYL CARBONATE POWDERS IN MICE

Particle Size	LD_{50} (95% Confidence Limits), mg./Kg.
Fine	1175 (1074–1502)
Regular	1775 (1573–2268)
Coarse	>2000[b]

[a] Data calculated by the logit chi-square method of Berkson (4). [b] Only 3/10 animals died at this dose.

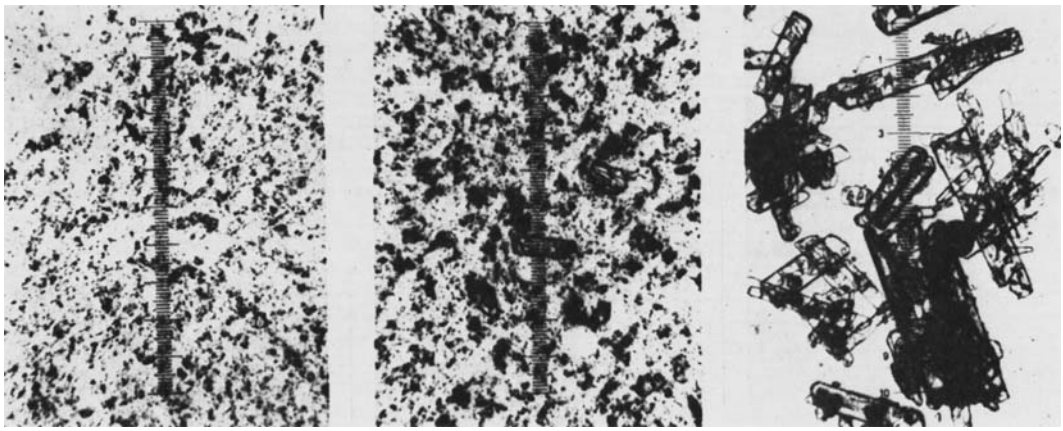

Fig. 1—Photomicrographs of the fine, regular, and coarse particle trichloroethyl carbonate used in this study (scale = 17.4 μ/small division).

The drug was prepared in three particle sizes as follows: fine particle, prepared by ball-milling a suspension of the drug in a 0.5% dispersion of gum tragacanth in water; regular particle, prepared by mixing a suspension of the drug in a 0.5% dispersion of gum tragacanth in water by

and a direct correlation was found between the oral LD_{50}'s and the peak blood levels of acetaminophen in the first 2 hr. Although no trichloroethanol blood levels were determined in this study on trichloroethyl carbonate, one might speculate that there would be a similar correlation between LD_{50}'s and peak trichloroethanol blood levels.

These studies indicate that when biologic mea-

[1] Clorethate, Smith Kline & French, Philadelphia, Pa.

surements are made on compounds that are relatively insoluble in water, the results have little meaning unless the particle size of the administered powder is taken into account.

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Keyphrases

Trichloroethyl carbonate—toxicity
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LD_{50} value—particle size effect

Books

REVIEWS

Potential Carcinogenic Hazards from Drugs. Evaluation of Risks. UICC Monograph Series, vol. 7. Edited by Rene Truhaut. Springer-Verlag, 1 Berlin 31 (Wilmsdorf), Heidelberger Platz 3, Germany, 1967. vii + 249 pp. 16.5 × 25 cm. Price DM 68,–; U.S. $17.00.

This is the seventh volume of the monograph series sponsored by the International Union Against Cancer. It consists of a series of 24 papers presented at a symposium of the Cancer Control Commission held in Paris, November 1965.

It is quite apparent from both the formal papers and the abbreviated versions of the discussions which follow that emphasis was placed on chemical contact or ingestion as the principal etiological factor in carcinogenesis. While this orientation may be justified in a symposium dealing with drugs, it must be recognized that there are many oncologists who subscribe to the view that chemical carcinogenesis is of only minor significance in relation to the incidence of human cancer.

The initial papers in the symposium deal with the present state of methodology for evaluating the potential carcinogenicity of drugs. The statistical assessment of data from the point of view of predictability is then discussed. In view of the law prohibiting the use of carcinogenic substances as food additives, it is interesting to note the view expressed by one of the participants, Prof. I. Berenblum, that "for all practical purposes, a carcinogen is, like any other noxious substance, only harmful above a certain critical dose level." In this connection, the opinion of Prof. H. Druckrey based on his analysis of the dose–time relationships of chemical carcinogenesis, is especially pertinent. He distinguishes between the primary effect of a carcinogen at the cellular or molecular level, and the subsequent multiplication of cancer cells to the point of tumor induction. As far as the primary effect is concerned he holds to the view that "there is no indication for the existence of a subthreshold dose." Nevertheless, he recognizes that a zero tolerance for carcinogens is "not always practicable and is scientifically objectionable" and proposes as a basis for future discussion that "1% of the lowest dosage which, given daily over the whole life span to susceptible experimental animals, produces cancer only at the end of the life span, can be considered as the maximum tolerable dose for human beings."

A number of papers in this volume deal more specifically with the potential carcinogenicity of specific classes of substances such as metal-containing drugs, petroleum hydrocarbons, lactones, and hormones including progesterone. In the two reports dealing with plastics used in orthopedic or surgical practice, as well as in the discussions of these papers, the weight of evidence is in support of a physical rather than chemical explanation of the carcinogenic effect of experimental implants.

In his remarks reflecting the point of view of the pharmacologist, Professor Alastair C. Frazer emphasizes the need for discrimination and judgment in deciding when a drug should be subjected to life-span study for potential carcinogenesis, and questioned the need for identifying "extremely feeble" carcinogenic drugs intended for use over short periods in people whose life expectancy is unlikely to provide time for any effect to be induced.

This monograph is required reading for those who wish to keep up with current thought among the experts in drug safety evaluation. Although the discussions following each presentation reveal the lack of unanimity on many aspects, there is agreement that much remains to be done to get at the root of these problems from both the methodological and interpretative standpoints.

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