Kinetics of Diphenylhydantoin Elimination in Rats

John J. Ashley\textsuperscript{1,2} and Gerhard Levy\textsuperscript{1}.

Received Aug. 17, 1972—Final Oct. 19, 1972

Concentrations of diphenylhydantoin (DPH) in the blood of male Sprague-Dawley rats after intravenous injection of 10 and 40 mg/kg \textsuperscript{14}C-DPH were determined over a sufficiently wide range to permit comparison of rates of decline at the same absolute and relative concentrations. This comparison leads to the conclusion that the elimination of DPH in the rat cannot be described by first-order or simple Michaelis-Menten kinetics but that it is qualitatively consistent with product inhibition of DPH metabolism.

KEY WORDS: diphenylhydantoin; elimination kinetics; product inhibition; dose-dependent kinetics.

INTRODUCTION

The elimination of the widely used anticonvulsant drug diphenylhydantoin (DPH) shows pronounced dose dependence in mice (1), rats (2), dogs (3), and man (4). Pharmacokinetic interpretation of this phenomenon has been limited appreciably by the lack of adequate drug concentration data over a sufficiently wide range to permit comparison of rates of decline of concentrations in the same absolute and relative concentration ranges in blood or plasma following different doses of DPH. One set of plasma concentration data following oral doses of 2.3, 4.7, or 7.9 mg/kg DPH for 3 days each to a single human subject has been fitted to the integrated form of the Michaelis-Menten equation, using the same $K_M$ and $V_m$ values (5). Similar data from rats, more limited in range, could not be fitted to the same $K_M$ and $V_m$ values (5). The study described here was carried out to obtain data for a more adequate assessment of DPH elimination kinetics in the rat.

\textsuperscript{1} Supported in part by grant GM 19568 from the National Institutes of Health.

\textsuperscript{2} On leave from the School of Pharmacy, University of Sydney, Sydney, Australia.
EXPERIMENTAL

Male Sprague-Dawley rats, weighing 250–360 g, received 10 or 40 mg/kg DPH (including 2 or 5 μC 14C-DPH) through a cannula inserted in the right external jugular vein. Blood samples were obtained over 140 min or 20 hr. DPH was extracted from the blood and assayed by liquid scintillation spectrometry. Details of the experimental methods and assay procedures have been described elsewhere (6).

RESULTS AND DISCUSSION

Average concentrations of DPH in the blood of five rats after a 10 mg/kg dose and in four rats after a 40 mg/kg dose are shown in Fig. 1. Averages and standard errors were obtained after logarithmic transformation of the data. The time course of relative concentrations (concentration/dose) is shown in Fig. 2. It is evident that the decline of DPH concentrations in the blood, in the same absolute and relative concentration ranges, is much slower after the larger dose. The dose-dependent difference in the same relative

![Graph](image)

Fig. 1. Concentration of diphenylhydantoin (DPH) in the blood of rats after intravenous injection of 10 mg/kg (●) and 40 mg/kg (○). Average of five and four rats, respectively. Vertical bars represent ± the standard error of the mean.