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Letters to the Editors

Amiodarone Disposition: Polyexponential, Power and Gamma Functions

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Dear Sir,

Description of pharmacokinetic data by power and gamma functions, as an alternative to the classical use of polyexponentials, has been advocated by Wise (1978, 1981). More recently, Weiss (1983) has emphasised some conceptual advantages of this approach with a view to "..stimulate data fitting by gamma curves in order to gain further experience of the value of this method in pharmacokinetic studies of particular drugs." Unfortunately, much of the drug data used to date to compare the suitability of the contending functions has been limited in its time-course and numbers of observations. There are also statistical problems in comparing 'goodness of fit' by different types of functions (Norwich and Siu 1982).

We have recently completed a study of the disposition kinetics of amiodarone, the kinetic properties of which seem well-suited to an exercise comparing the fitting of polyexponential and power functions to plasma drug concentration – time data. Thus, continually convex-decreasing plasma concentrations of amiodarone, covering a 10,000-fold range, were observed up to 84 days (median 67 days) after a 10-minute i.v. infusion of 400 mg of the drug (Holt et al. 1983 a, b).

The following functions were fitted to the data by nonlinear least squares regression analysis using both NONLIN (Metzler 1974), with each observation weighted by the reciprocal of the square of its value, and ELSFIT (Sheiner 1983):

1. A polyexponential function:

$$C = \sum_{i=1}^{n} C_i \cdot e^{-\lambda_i \cdot t} \text{ where } n = 3 \text{ or } 4$$

2. A power function:

$$C = A \cdot t^{-a}$$

3. A gamma function:

$$C = A \cdot t^{-a} \cdot e^{-bt}$$

Concordant results were obtained using NONLIN and ELSFIT. Of the two polyexponential functions tested the four-term equation was superior to the three-term equation in 5 of the 6 subjects, based on the *F*-test (0.05 level of significance) and the Akaike information criterion (Yamaoka et al. 1978). These tests cannot be applied directly to compare fits by the other functions with those of the polyexponential functions (Norwich and Siu 1982). Therefore, in these cases the criteria of Schwarz (1978) and Leonard (1979) were applied showing that better fits were obtained with the polyexponential functions. Judgement of 'goodness of fit' was also based upon inspection of the weighted residuals and graphical representations of the data. A simple diagnostic test involves plotting the observed and predicted data on log-log paper when a polyexponential function gives an oscillatory plot, a power function gives a straight line and a gamma function gives a straight line followed by a downward curving phase. In each subject such plots clearly indicated the superiority of the polyexponential fits to the data over those afforded by the power and gamma functions. Representative plots for one subject are shown in Fig. 1.

We conclude that, in the case of amiodarone, the classical method of data description is preferable despite the theoretical attractions of the power/gamma function approach.

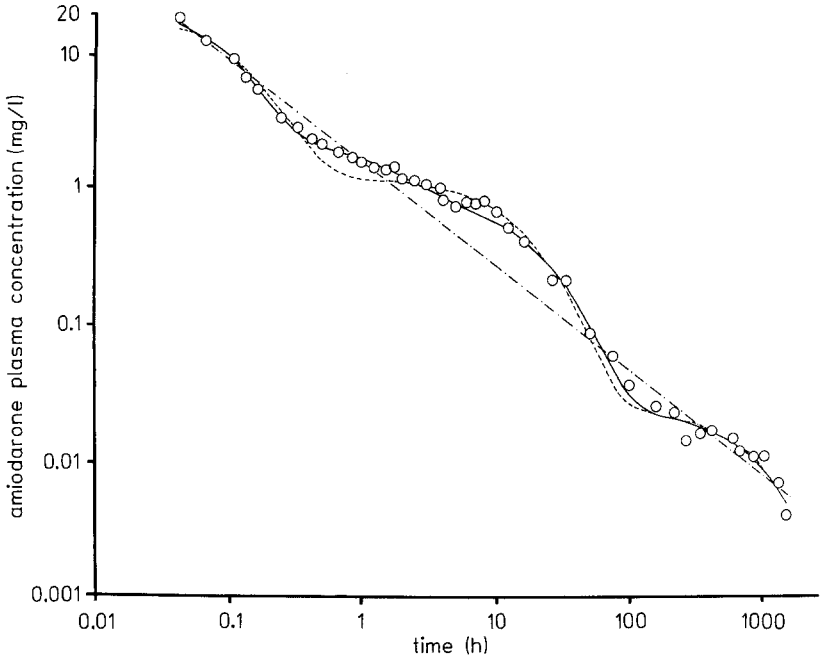

Fig. 1. Log-log plot of plasma drug concentration after a 400 mg i.v. infusion of amiodarone over 10 min in a normal subject. (0 experimental data; – – – – 3-term polyexponential fit ($C = 19.2 \cdot e^{-8.06t} + 1.20 \cdot e^{-0.064t} + 0.027 \cdot e^{-0.0011t}$); —— 4-term polyexponential fit ($C = 23.4 \cdot e^{-12.02t} + 1.57 \cdot e^{-0.657t} + 0.82 \cdot e^{-0.0489t} + 0.254 \cdot e^{-0.0011t}$); – · – · – power function fit ($C = 1.55 t^{-0.76}$). The gamma function fit ($C = 1.56 t^{-0.75} \cdot e^{-0.0002t}$) was similar to that of the power function except for curvature through the last two data points. NONLIN was used to obtain these fits

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