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CONCENTRATION EFFECT MODELLING WITH CONVERTING ENZYME INHIBITORS IN MAN

The investigation of pharmacokinetic and pharmacodynamic relationships after converting enzyme inhibitors has been limited up until now. The drug most widely available, captopril, cannot be easily or accurately measured in plasma because of the presence of diamers and condensation products with endogenous compounds (Kripalani *et al.*, 1980). In addition, measurement of plasma converting enzyme activity after captopril must be done immediately if under-estimates of inhibition are to be avoided (Roulston *et al.*, 1980).

We read with interest the paper by Biollaz *et al.* (1982), in which the authors related the inhibition of plasma converting enzyme to drug plasma levels following single oral doses of other converting enzyme inhibitors, enalapril maleate (MK421), and the lysine analogue (MK521). In both cases the extent of inhibition (expressed as a percentage of pre-drug levels) was related to log plasma drug concentration. A close correlation was observed for the group. However, since the % inhibition, I, is calculated as:

$$I = (1 - \frac{A_t}{A_o}).100$$

the maximum possible value of I is 100, a fact which is not reflected in the regression analysis. Also, it would seem practical to analyse the data for each individual separately to get an estimate of the between subjects variability of the relationship. The method described in the paper ignores the repeated measures from 12 individuals and may thus overestimate the degrees of freedom.

We would like to report on an extension to the analysis of similar data which have been previously described (Millar *et al.*, 1982). The data were more limited, in that only six data points for inhibition and plasma concentrations were available for nine subjects. We would propose that it may be more appropriate to analyse the results for each subject using a Hill type function, with the usual maximum response set to 100 where

$$I = \frac{100\,[C]^{\gamma}}{[C^{\gamma}_{50}] + [C]^{\gamma}}$$

Drug concentrations and different degrees of inhibition are known and thus the values of the parameters γ and C_{50} can be obtained. The interpretation of the parameters is that γ reflects the gradient of the inhibitory effect-drug concentration curve, and C_{50} is the concentration of converting enzyme inhibitor required to produce 50% maximal response. Satisfactory fits were obtained in all but one data set, and in the other 17 sets a significantly better fit was obtained than that using the log transformation technique. The individual parameter values are tabulated (Table 1), together with the coefficient of determination (r^2).

Table 1 Values for γ and C_{50} for individual data sets

	MK421			*MK521*		
Subject	γ	C_{50}	r^2	γ	C_{50}	r^2
1	1.11	10.3	0.96	0.53	0.77	0.98
2	0.58	2.57	0.83	0.39	0.08	0.99
3	0.55	1.62	0.99	0.35	0.05	0.99
4	1.18	2.77	0.94	1.19	5.33	0.93
5	0.61	4.18	0.98	0.67	2.00	0.99
6	1.07	38.7	0.97	0.65	1.98	0.97
7	—	—	—	0.42	0.39	0.99
8	0.71	5.08	0.99	0.34	0.71	0.99
9	0.91	6.78	0.99	0.34	0.09	0.98

r^2 = coefficient of determination for each data set $n = 6$.

The Hill function probably represents a more physiological relationship between plasma drug concentration and plasma converting enzyme inhibition than the log concentration relationship, and also models the fact that there is an upper limit to the pharmacological effect. It would be interesting to analyse the more extensive data for each subject in the study of Biollaz *et al.* (1982) as outlined above.

The determination of parameters of converting enzyme-inhibitory response in individuals after acute dosing could be compared with chronic dosing to determine whether the gradient of the relationship or the C_{50} changes with time or differs in different patient groups.

Concentration effect modelling to include the rela-

tionships between plasma renin activity, plasma angiotensin II levels and indeed blood pressure fall might clarify the controversial and contradictory reports (Waeber *et al.*, 1980; Boomsma *et al.*, 1981; Atkinson *et al.*, 1982), where captopril was used and simple linear or log linear regression was undertaken.

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