DESIGN AND ANALYSIS OF THE AMINOPYRINE BREATH TEST

A.Z. Khan, L. Aarons, Dept. Pharmacy, University of Manchester, Manchester

Aminopyrine (AP) is sequentially N-demethylated by the hepatic microsomal enzyme system to form monomethylamino-antipyrine (MAP) and then aminoantipyrine (AA), with carbon dioxide being the final product of both the demethylations. By monitoring carbon dioxide production after administration of (N-dimethyl ^{14}C) aminopyrine the demethylation rate of this drug can be used as a non-invasive indicator of the activity of hepatic drug metabolising enzymes in animal and human investigations.

The CO_2 exhalation rate (CER)-time profile may be described by a biexponential equation (Rhodes et al 1982) where the exponents represent the rate constants for the two demethylation steps (K_1 and K_2) and the coefficients are a function of K_1 and K_2 and the fractions of AP and MAP undergoing demethylation. The equation reduces to a single exponential when the ratio of K_2 to K_1 (K) approaches either 0.5 or zero. Consequently under certain conditions it is difficult to resolve the exponentials representing the two demethylation steps.

Simulation studies were carried out in order to determine the conditions under which fitting a biexponential equation to data would be more appropriate than a monoexponential function. A sequential approach was compared with using a fixed number of equally spaced time points. Data were generated using the described biexponential function and random noise (normal distribution : mean zero and standard deviation σ) was added. In the sequential method five data points were generated for normalised sampling times spaced logarithmically between zero and ten. If there was a significant preference for the biexponential equation at this value of N (the number of data points), then the experiment was terminated. Otherwise another point was generated using the information from the existing data points to allow maximum discrimination between the equations. A maximum of twenty points per experiment were allowed and experiments were carried out for various values of σ and K (Table 1). This sequential approach was then compared with using a fixed number of equally spaced points.

Table 1. Results of the sequential analysis of the AP Breath Test.

K	0.3	0.3	0.3	0.4	0.4	0.4	0.45	0.45	0.45
σ	0.01	0.025	0.05	0.01	0.025	0.05	0.01	0.025	0.05
N	6	9	10	8	13	14	12	13	>20

It can be seen from Table 1, that as the values of K and σ increase, more and more data points are required to decide whether a biexponential function gives a more appropriate fit. When the sequential approach was compared with using equally spaced points, then on average fewer points were always required for the former, in order to obtain a significant preference for the biexponential equation (e.g. at K = 0.4 and σ = 0.05 the fixed point approach could not differentiate between the two equations even at N = 20). The difference between a monoexponential and a biexponential fit is small when K is near zero or 0.5 and increases gradually as we move away from these two extreme values. Therefore there exists an optimum value of K for the purpose of discriminating between the two functions. The maximum absolute difference between the area under the biexponential fit to that under the monoexponential was used to locate this value and was found to be 0.1.

These findings may have implications on the way data from the AP breath test is analysed and also the choice of the equation that is used for this purpose. When K has a value near 0.5 or zero then the difference between the two equations is so small that the data can be adequately described by a monoexponential equation. Thus, even though the demethylation rate constants differ by a factor of two it may be difficult to obtain precise estimates of them.

Rhodes, J.D., Aarons, L.J. and Houston, J.B. (1982). Br. J. Clin. Pharmac. 14: 409-414.