A new polyalgorithmic method for time-course analysis of pharmacological data describable by a multiexponential function

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In a previous communication (Cavero, Gomeni, Lefèvre & Roach, 1978) it was reported that the analysis of the time-course of a biological response should be preferred to that of the peak effects.

In this demonstration, a new method to determine parameters defining time-effect profiles describable by a multiexponential function will be presented.

Figure 1 indicates the essential parameters needed to describe a time-effect (E) profile representable by a biexponential equation. The peak effect and the time needed to reach it (t_{max}) are given by the experimental values. The phases of onset and decay are well characterized by calculating the rate constants (α and β) using the biological data and the time of their occurrence. A modular Fortran programme allows the determination of the order (number of exponentials) of the model as well as the initial parameter estimates by an objective criterion using a modification (stepwise determination of the order) of the repeated integration method (Foss, 1971; Nieman, Fisher & Seborg, 1971). Then, the Harthley modified Gauss–Newton method is used to find the values of the best fitting parameters (Hartley, 1961).

Statistical tests used to judge the acceptability of the model for describing the experimental data (goodness of fit) are the correlation coefficient, the Kolmogorov–Smirnov test, chi^2 and run test.

Since the experimental values can be affected by a randomly distributed error (e.g. investigator, instrumentation, etc.), the programme provides several widely used methods to weight the data.

Other parameters given by the computer program are the apparent half lives of each phase (e.g., onset, distribution, decay), the cumulative area under the experimental data points using the trapezoidal rule (AUC_e), the area extrapolated to infinity (AUC_t) using the half life and the last data point and the gravity duration which is the time needed to reach the baricentre of the curve.

Application of this new polyalgorithm to the heart rate and blood pressure effects of several doses of clonidine (1.0–50.0 μg/kg, i.v.) in the pithed rat with an experimentally induced tachycardia (Cavero *et al.*, 1978) will be shown.

References

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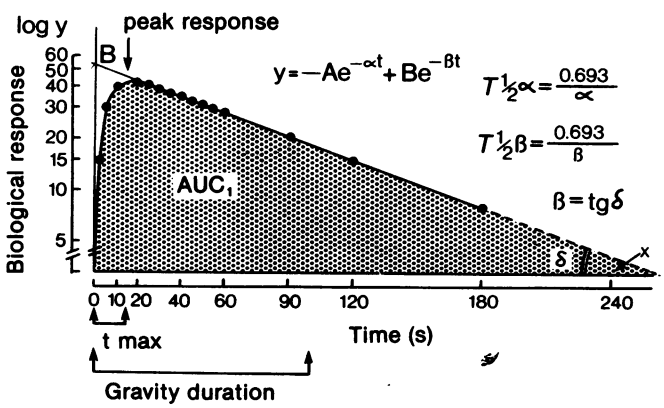

Figure 1 Parameters and equation describing the biological effect as function of the time.