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A refined procedure for determining pA_2 values

pA_2 Values (Schild, 1947; Arunlakshana & Schild, 1959) are widely used to quantify the affinity of antagonists for a receptor site and also to characterise receptor types *in vitro*. Recently, this method has been used to measure "apparent" pA_2 values *in vivo* (Hayashi & Takemori, 1971). The method is based on a plot of $\log_{10}$ (dose ratio -1) against $-\log_{10}$ molar concentration of antagonist. However, this procedure does not make the best use of all the available information and may lead to inaccuracies in the estimation of pA_2. We present a new procedure for measuring pA_2 values that does not possess these disadvantages.

The method of Schild is to estimate the parameters α (intercept on the ordinate) and β (slope) of the straight line:—

$$\log_{10}\left(\frac{C_m}{C_0}-1\right) = \alpha + \beta \log_{10} M \quad .. \quad .. \quad .. \quad (1)$$

where C_0 is the dose (mg litre^{-1} *in vitro* or mg kg^{-1} *in vivo*) of the agonist alone which causes 50% of the response being measured (ED50 value) and C_m is the ED50 value of the agonist in the presence of M mol litre^{-1} *in vitro* or M mol kg^{-1} *in vivo* of antagonist. Thence pA_2 is given by:—

$$pA_2 = \frac{\alpha}{\beta} \quad .. \quad .. \quad .. \quad .. \quad .. \quad (2)$$

Although equation (1) is linear and therefore amenable to elementary treatment, the direct relationship between the potency of the agonist (C_m) and the molar concentration of the antagonist (M) is not linear. The direct relationship which is obtained by rearrangement of equation (1) is:—

$$C_m = C_0'(1 + 10^{\alpha} M^{\beta}) \quad .. \quad .. \quad .. \quad .. \quad (3)$$

where all the symbols have the same meaning as in equation (1) except that C_0' is the estimate of the ED50 value for the agonist alone. The pA_2 is derived from equation (2) as before. The advantages of using equation (3) to determine pA_2 values instead of equation (1) are illustrated by reference to Fig. 1.

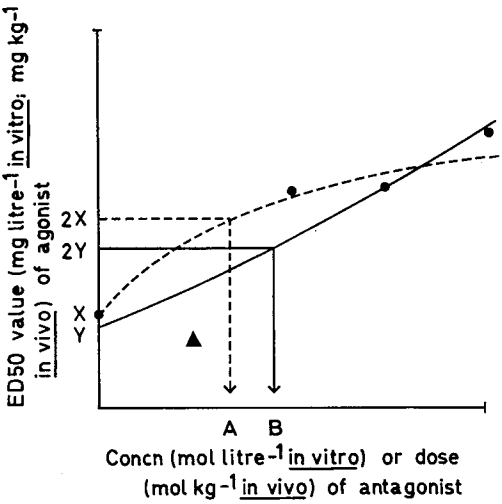

FIG. 1. Using fictitious exemplary data (● and ▲) on arbitrary scales, curves are shown as calculated from equation (1) (- - - -) and from equation (3) (———). The *assumed* value of C_0 *for* equation (1) is X and $-\log A$ is its corresponding pA_2. The point ▲ has to be ignored as it is less than X. The *estimated* value of C_0' *from* equation (3) is Y and $-\log B$ is its corresponding pA_2.

Thus:—

1. Using equation (1) the ED50 value C_0 is *assumed* to be known (intercept X on the ordinate of Fig. 1) whereas it is in fact obtained by measurement as are the ED50 values for each C_m.

2. Using equation (1) it is not always possible to use all the data since, to be used, each C_m must be greater than C_0 for $\left(\frac{C_m}{C_0}-1\right)$ to be positive. Moreover, using equation (1) there is a bias towards overestimation of the pA_2 since a value of C_m is more likely to be ignored when C_0 is above rather than when it is below its true value.

All the disadvantages of determining pA_2 values using equation (1) are overcome by using equation (3). Since the availability of computers makes it easy to fit the non-linear equation (3) to experimental data this improved procedure should have wide application for the study of drug antagonism and receptor type both *in vitro* and *in vivo*.

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