Graphic Differentiation between Competitive and Functional Synergism

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SUMMARY

A graphic method is presented which permits one to differentiate between otherwise indistinguishable dose-effect plots of drugs displaying competitive synergism (both drugs acting on the same receptor) and functional synergism (drugs acting on different receptors linked to the same effector system).

The terms "competitive synergism" and "functional synergism" refer to the effect of the combination of two similarly acting drugs; in the former case these drugs act on the same receptor (1), in the latter on different receptors which operate through the same effector system (2). The respective equations (Eqs. 1 and 2) are

$$E_{AB} = \frac{\alpha r K_B[A] + \beta r K_A[B]}{K_B[A] + K_A[B] + K_A K_B} \quad (1)$$

and

$$E_{AB} = \frac{\alpha r_A}{\frac{K_A}{[A]} + 1} + \frac{\beta r_B}{\frac{K_B}{[B]} + 1} - \frac{\frac{\alpha r_A}{\frac{K_A}{[A]} + 1} \cdot \frac{\beta r_B}{\frac{K_B}{[B]} + 1}}{E_{max}} \quad (2)$$

where E_{AB} is the effect of the drugs A and B in combination, α and β are the intrinsic activities of the two drugs, K_A and K_B are their dissociation constants from their receptors, r in the first equation and r_A and r_B in the second are the total concentrations of the respective receptors, and E_{max} the maximal response of which the effector system is capable. These symbols, terms, and equations follow the presentation of Ariëns *et al.* (1, 2).

As Ariëns points out (3), the customary technique of identifying the character of the interaction of two drugs (plotting dose-response curves for one drug at several constant concentrations of the other) fails in this instance when the intrinsic activities of the two drugs are approximately the same: in that case both types of drug interaction yield plots of the same appearance. The reason for this failure is that, when [B] is kept constant, Eqs. 1 and 2 are both reduced to the form $E_{AB} = ([A] + K_1)/(K_2[A] + K_3)$, where the constants K_1, K_2, and K_3 contain the several parameters of Eqs. 1 and 2. Thus in both cases similar graphs are obtained; and since not all the parameters can be known, it is also impossible to distinguish between the two mechanisms in question by the numerical values of the variables.

Nevertheless, a different approach can make these graphs yield the desired information. It is easily seen that, when not [B] but E_{AB} is kept constant and [A] and [B] are the variables, Eq. 1 becomes linear and Eq. 2 hyperbolic. What is needed, therefore, is to draw isobolic lines (straight lines perpendicular to the E_{AB} axis) and to note their intersections with the dose-effect curves. Next, the concentrations of the two drugs at these points of intersection are plotted against each other. If, for the points along each isobole, linear plots are obtained, the

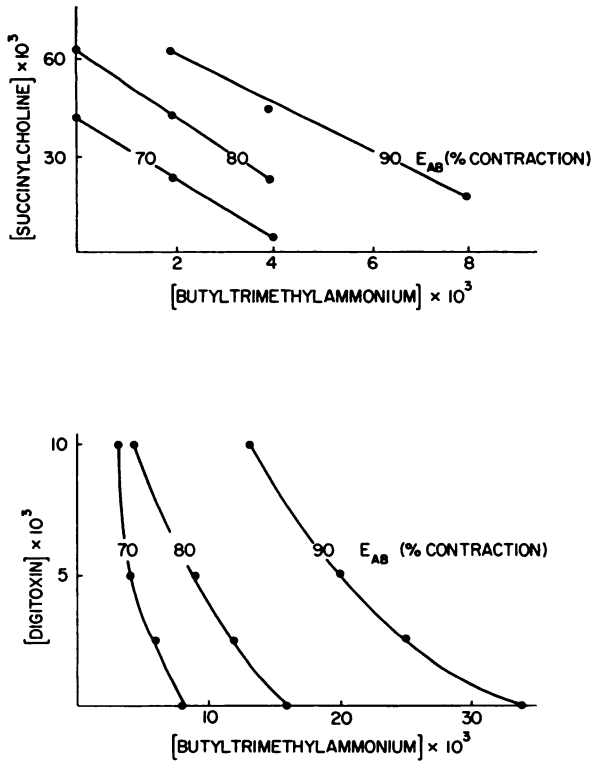

FIG. 1. *Isoboles (at 70, 80, and 90% contraction) for the contraction of frog rectus muscle by the drug pairs succinylcholine-butyltrimethylammonium (top) and digitoxin-butyltrimethylammonium (bottom).* After Ariëns (3).

synergism is competitive; otherwise it is functional.

Ariëns illustrates the problem of differentiating between these two types of synergism with the examples of succinylcholine and butyltrimethylammonium on the one hand, and butyltrimethylammonium and digitoxin on the other (3). All three drugs contract the frog rectus muscle, but it is reasonable to presume that the synergism between succinylcholine and butyltrimethylammonium is competitive, since these two drugs are opposed in their action by the same competitive antagonists, while digitoxin and butyltrimethylammonium have no such common antagonist, so that their common action should proceed by different receptors. The dose-effect plots for the two pairs of drugs are, as expected, indistinguishable (3). When, however, the graphic procedure outlined in the preceding paragraph is applied to these plots, the difference between them becomes apparent and the postulated mechanisms are confirmed since, as shown in Fig. 1, linear plots result for the synergism of the two quaternaries, and hyperbolic plots for the synergism between butyltrimethylammonium and digitoxin.

REFERENCES

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