Non-additive anaesthetic effects of alphaxalone and methohexitone

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In 1937 Meyer suggested that the correlation between the anaesthetic potency of a substance and its lipid solubility could be summarized as follows: anaesthesia commences when any chemically indifferent substance has attained a certain molar concentration in the lipids of the cell; this concentration depends on the species but is independent of the nature of the anaesthetic. Subsequently Mullins (1954) proposed that anaesthesia commences when a certain critical volume fraction of anaesthetic has been achieved in the cell membranes. Both hypotheses predict that the effects of combinations of anaesthetics should be additive. This has been verified with mixtures of gaseous and volatile anaesthetics (Miller, Wahrenbrock, Schroeder, Knipstein, Eger & Buechel, 1969). To test this prediction for non-volatile anaesthetics we chose to investigate the anaesthetic potencies of mixtures of short-acting intravenous anaesthetics.

Male Wistar rats (150–200 g) received, into the tail vein, injections of methohexitone, alphaxalone or alphadalone acetate either alone or as mixtures of two compounds. The duration of the loss of righting reflex was recorded. Each rat received only one injection.

Rats injected with either alphaxalone (3 mg/kg), alphadalone acetate (12 mg/kg) or methohexitone (12 mg/kg) lost their righting reflex for about 8 minutes. Rats injected with a mixture of alphaxalone (1.5 mg/kg) and alphadalone acetate (6 mg/kg) also lost their righting reflex for about 8 min as predicted by the theories. However, rats injected with a mixture of alphaxalone (1.5 mg/kg) and methohexitone (6 mg/kg) lost their righting reflex for about 11 min (see Fig. 1).

These behavioural results are supported by unpublished electrophysiological observations with similar mixtures which have shown that alphaxalone potentiates the depressant action of methohexitone and other barbiturates on synaptic transmission in isolated preparations of olfactory cortex. Therefore the potentiation between methohexitone and alphaxalone presumably reflects a specific drug interaction within the central nervous system. These results are not compatible with either the simple lipid solubility hypothesis of Meyer or with the critical volume hypothesis of Mullins.

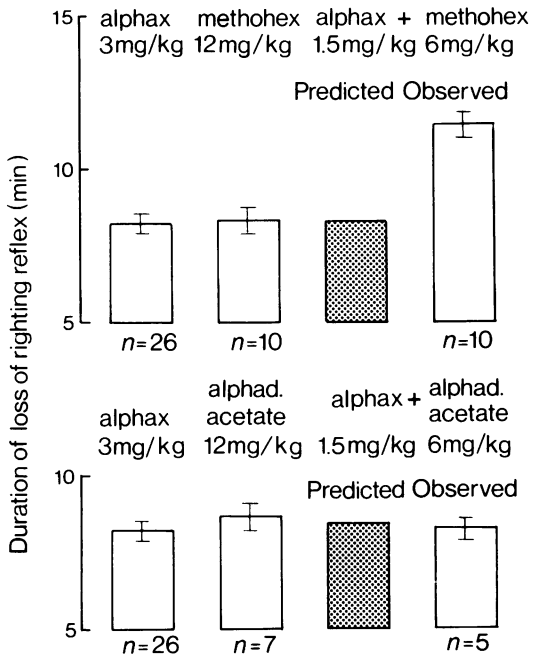

Figure 1 The height of each column represents the mean duration of the loss of righting reflex (±s.e. mean) produced by i.v. injection of anaesthetic or combination of anaesthetics shown above. The duration of the loss of righting reflex caused by a mixture of alphaxalone and methohexitone was significantly longer than that produced by either anaesthetic given alone ($P < 0.001$ by 2 tailed t-test).

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References

MEYER, K.H. (1937). Contributions to the theory of narcosis. *Trans Faraday Soc.*, **33**, 1062–1064.

MILLER, R.D., WAHRENBROCK, E.A., SCHROEDER, C.F., KNIPSTEIN, T.W., EGER, E.I. & BUECHEL, D.R. (1969). Ethylene-halothane anaesthesia: addition or synergism? *Anesthesiology*, **31**, 301–304.

MULLINS, L.J. (1954). Some physical mechanisms in narcosis. *Chem. Rev.*, **54**, 289–323.

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