RELATIONSHIP BETWEEN RATE OF ELIMINATION OF TUBOCURARINE
AND RATE OF DECLINE OF ITS PHARMACOLOGICAL ACTIVITY

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SUMMARY

It is shown on theoretical grounds that, assuming tubocurarine elimination is an exponential process and the intensity of its pharmacological activity is proportional to the logarithm of the dose, the decline of activity is likely to be linear with time. This conclusion is supported by clinical data.

The design of rational dosage schedules of tubocurarine to obtain sustained muscular relaxation has recently been described by Ryan (1964). His paper dealt primarily with the time course of tubocurarine concentration or amount in the body; it is intended here to consider the time course of tubocurarine activity.

Let it be assumed that the intensity of pharmacological activity of tubocurarine is related linearly to the logarithm of the body drug content (dose). This is a common finding with most drugs and applies over a considerable range of pharmacological activity. In mathematical terms

\[ I = m \log A + i \]  

(1)

where \( I \) is the intensity of pharmacologic activity, \( A \) is the amount of tubocurarine in the body, \( m \) is the slope of the line when \( I \) is plotted against \( \log A \), and \( i \) is the intercept of the line on the \( I \) axis.

Assuming exponential disappearance of tubocurarine from the body,

\[ \log A = \log A_0 - \frac{K}{2.3} t \]  

(2)

where \( A \) is the amount of tubocurarine in the body at time \( t \), \( A_0 \) is the intercept at zero time of the extrapolated linear portion of a plot of \( \log A \) versus \( t \), and \( K \) is the first-order elimination rate constant for tubocurarine.

Equations (1) and (2) may be combined (Levy, 1964) to yield

\[ I = I_0 - \frac{Km}{2.3} t \]  

(3)

which indicates that the pharmacologic activity of tubocurarine should decline linearly (rather than exponentially) with time. This is indeed the case, as shown in figure 1 (based on data from Bellville, Cohen, and Hamilton, 1964), which depicts tubocurarine plasma concentration and...
degree of muscular relaxation (determined on the basis of decrease in grip strength) as a function of time. It is evident that drug concentration decreases exponentially, and activity decreases linearly (i.e., at a constant rate), with time. This is contrary to the frequently expressed assumption that the change of pharmacologic activity with time parallels that of drug concentration or body drug contents.

REFERENCES

INTERATIONAL SYMPOSIUM
on Interactions between drugs used in preparation for surgical operations and anaesthesia
September 1966—Recoaro Terme (Vicenza)—Italy.

In September 1966 an International Symposium will be organized to discuss interactions which may occur between the drugs employed in the preparation of patients for surgical operations and anaesthesia. (Drugs pertaining to pre-anaesthesia are excluded).

The meeting will be based only on panel discussions (reports are not allowed) and will deal with the following subjects: Antibiotics; Hormones; Analgetics; Psychotropes; Cardiokinetics and diuretics; Cardiotonics and analeptics; Hypotensors and ganglioplegics; Vasoconstrictors; Hydrotherapy.

Simultaneous translations will be performed in French, English, Italian and German.

A prospectus will be sent by the end of January 1965.

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