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

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

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,

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

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

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

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


RAPPORT ENTRE LE RYTHME D'ELIMINATION DE LA TUBOCURARINE ET LA RAPIDITE DE DISPARITION DE SON ACTIVITE PHARMACOLOGIQUE

SOMMAIRE

On montre par des arguments theoriques qui si l'on admet que l'elimination de la tubocurarine est un processus exponentiel et que l'intensite de son activite pharmacologique est proportionnelle au logaritme de la dose, la disparition de son activite est probablement en relation lineaire avec le temps. Cette conclusion est confirmee par des donnees cliniques.

BEZIEHUNG ZWISCHEN DER AUSSCHEIDUNGS-RATE DES TUBOCURARINS UND DER RATE DES ABFALLES DER PHARMAKOLOGISCHEN WIRKSAMKEIT

ZUSAMMENFASSUNG

Aufgrund theoretischer Erwagungen, wobei angenommen wird, dafl die Elimination des Tubocurarins ein Exponentialprozess darstellt und die Intensitat der pharmakologischen Wirksamkeit dem Logarithmus der proportional verlaflt, wird festgestellt, dafl der Wirksungsabfall wahrscheinlich linear zur Zeit verlaflt. Diese Annahme wird durch klinische Ergebnisse unterbaut.

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