TUBOCURARINE ADMINISTRATION BASED UPON ITS DISAPPEARANCE AND ACCUMULATION CURVES IN ANAESTHETIZED MAN

BY

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SUMMARY

A method is described which results in smooth curarization and prompt recovery using minimal amounts of tubocurarine. Following an initial dose, usually 15 mg, paralysis is maintained by a continuous infusion delivering an amount per hour about equal to the initial dose. From a mathematical interpretation of this statement an equation for the exponential disappearance of tubocurarine from the extracellular water can be obtained. Controlled ventilation is used with a light level of halothane anaesthesia. No supplementary injections of anaesthetic or analgesic are necessary. Reversal with neostigmine is prompt and complete. The accumulation curve of tubocurarine has been described and its applications stated. The time required for it to reach equilibrium between the plasma and interstitial fluid has been calculated. At any time following single or multiple doses of tubocurarine, the quantity remaining in the extracellular water may be determined from the equations; this also applies to tubocurarine delivered by infusion.

Sustained muscular relaxation produced by a continuous infusion of non-depolarizing relaxant was first used by Evans and Spencer Gray (1953), who advocated the use of a mixture of thiopentone and gallamine; respiration during all cases was spontaneous. Gallamine alone was similarly employed by McIntyre (1953) in the treatment of tetanus. Kirkpatrick, Glossop and McCormick (1956), using a laudexium infusion, successfully treated a case of tetanus by means of complete paralysis and artificial pulmonary ventilation over a period of sixteen days.

Following an intravenous dose of tubocurarine, the decline in the plasma concentration takes place in two phases (Utting, 1963). There is an initial phase in which the rate of decline is rapid and is due to tubocurarine leaving the plasma and entering the interstitial fluid. After 10 to 20 minutes, equilibrium of tubocurarine between the plasma and the interstitial fluid is reached and the rate of decline is much slower.

This paper deals mainly with the slow phase of decline. The use of a tubocurarine infusion to maintain an initial dose of the drug during major surgery is described. The equations and graphs refer to the amount of tubocurarine in the extracellular water, i.e. plasma and interstitial fluid. Absolute amounts of tubocurarine in mg are used, rather than concentration levels, in order to preserve a practical understanding for clinical use. In this way one may keep track of an initial dose and maintain this amount, if desired, by tubocurarine infusion. The degree of paralysis is parallel with this amount of tubocurarine; this is true at all times, except after the use of neostigmine, and of course at zero time \( t=0 \), when one must wait the usual 1 to 2 minutes for the initial dose to become effective. The amount remaining after a period of time can be estimated and then reversed with neostigmine, which is the anti-curare drug of choice and is recommended as a routine and integral part of tubocurarine administration (Sellick, 1955).

METHOD

Anaesthesia is induced with thiopentone, 250–500 mg, followed by suxamethonium, 50–100 mg. A cuffed tube is passed and controlled ventilation is performed manually by compression of the reservoir bag, using a non-return valve (Ryan, 1955).
A 50 per cent oxygen-nitrous oxide mixture with halothane, 0.5 per cent, is given to maintain a light level of anaesthesia.

A tubocurarine infusion, 30 mg in 500 ml 5 per cent dextrose, is then set up to deliver 15 mg per hour (about 60 drops/minute). When the succinylcholine paralysis ceases, the initial dose of tubocurarine 10–15 mg is injected into the drip tubing. More may be added during the next few minutes, either by injection or by increasing the infusion rate; if the initial dose is considered excessive, the rate may be decreased. The maximum total initial dose is 20 mg. The degree of relaxation, judged by the feel of the reservoir bag during inflation of the lungs, is controlled by the rate of tubocurarine administration. No other injections of anaesthetic or analgesic drugs are necessary at any time when this method is in use.

About 25 minutes before the end of the operation the tubocurarine infusion is replaced by one of 5 per cent dextrose. Fifteen minutes after this, residual effects are reversed using atropine, 1.2 mg, and neostigmine, 5 mg.

After about fifty administrations with this method, it became apparent that a relationship existed between the initial dose and the rate of the infusion required to maintain the effect of this dose. In general, satisfactory paralysis could be maintained by an infusion delivering per hour an amount equal to the initial dose.

Tubocurarine was then given in this way to 240 adult patients. The initial dose was 15 mg in about half this number, and was maintained by administration of 15 mg/hour. The infusion rate remained constant during operations lasting up to 2½ hours. In longer operations the maintenance dose by infusion continued to be fairly constant in 70 per cent of the patients. In the remaining long operations where there was often extensive surgery associated with moderate blood loss which was replaced, the rate of infusion, which had been constant earlier, delivering, say, 15 mg/hour for the first 2 hours, had to be reduced slightly toward the end of the operation to deliver about 10 mg/hour. Reversal with atropine and neostigmine was prompt and complete in all cases.

**GRAPHICAL PRESENTATION**

While the remarks in this section apply to any initial dose between 10 and 20 mg, it will be convenient to consider a specific initial dose of, say, 15 mg. The curves shown in figure 1 are derived from the mathematical interpretation of the data using methods explained in the following section.

The intensity of paralysis depends upon the concentration of tubocurarine at the neuromuscular junction. This, in turn, depends upon the concentration in the plasma and interstitial fluid (Foldes, 1959). An initial dose of, say, 15 mg produces the effective concentration and paralysis; this is shown as OA in figure 1. This concentration will decline according to curve AB if no additional drug is given. However,
when an infusion is started at A, the initial dose level of 15 mg in the plasma and interstitial fluid can be maintained along AC, and the paralysis will be sustained, when the rate of infusion equals that of disappearance.

When the infusion is stopped at C, the remaining tubocurarine will disappear along curve CD.

Fifteen minutes after this, atropine and neostigmine are given at E. Neostigmine develops its full effect in 2 to 4 minutes, and this intensity is maintained for 30 to 45 minutes (Foldes, 1960); it then slowly disappears in 3 to 5 hours (Ferguson, 1962). During this time the remaining tubocurarine no longer produces paralysis and continues to disappear along curve CD.

MATHEMATICAL INTERPRETATION

When it was found, in fact, that satisfactory paralysis could be maintained by a tubocurarine infusion delivering per hour an amount equal to the initial dose, an equation was sought that would satisfy this relationship.

Throughout this paper it will be assumed that the rate of disappearance of tubocurarine from the combined plasma and interstitial fluid is proportional to the amount of the drug in this combined compartment, then the process will be exponential and may be represented by the equation:

\[ C = C_0 e^{-kt} \]  

(1)

where \( C \) is the amount of tubocurarine in the plasma and interstitial fluid in mg at time \( t \) in hours, and \( C_0 \) is the initial dose in mg. When the value of the constant, \( k \), is found the exact shape of the disappearance curve, AB in figure 1, will be determined. To do this it is necessary to state that the rate of disappearance, in mg/hour, at any instant is given by the derivative of equation (1), and is:

\[ \frac{dC}{dt} = -kC \]  

(2)

In this equation when \( t=0 \), \( C = C_0 \). It is also known that when \( t=0 \), the rate of disappearance of tubocurarine, \( \frac{dC}{dt} \), is equal to the rate at which it is being put in by infusion, \( C_0/\text{hour} \), but negative. The rate of disappearance is therefore \(-C_0/\text{hour}\), and equation (2) becomes:

\[ -C_0 = -k(C_0) \]

and \( k=1 \). Substituting this value of \( k \) into the general equation (1) we obtain:

\[ C = C_0 e^{t} \]  

(3)

By letting \( C \) in equation (3) equal \( \frac{1}{2}C_0 \) we can calculate the half-life of tubocurarine in the plasma and interstitial fluid; it is 42 minutes. This time value is supported by Pelikan and associates (1950) who found in a pharmacological study of conscious subjects, that after 45 minutes a second injection of half the initial dose gave the same effect as the full initial dose. Furthermore, Kalow (1953) found from the theoretical analysis of the excretion rates of tubocurarine that the half-life in the extracellular fluid should be 45.6 minutes; Kalow (1959) also found that the plasma curves of tubocurarine published by Pittinger, Morris and Cullen (1951), Marsh (1952), Cohen, Paulson and Elert (1957), and Aladjemoff, Dickstein and Shafir (1958), were compatible with this figure.

From this analysis it may probably be concluded that the process of tubocurarine disappearance from the combined plasma and interstitial fluid is exponential and is represented by equation (3). The curve AB in figure 1 is obtained from equation (3) when \( C_0 = 15 \text{ mg} \).

ACCUMULATION CURVE

Gaddum (1944) has shown that the curve of accumulation is identical with the curve of disappearance but inverted, and is described by the equation:

\[ C = C_\infty (1 - e^{-kt}) \]  

(4)

This equation applies when tubocurarine is given continuously at a constant rate. \( C \) is the amount of drug in the plasma and interstitial fluid in mg at time \( t \) in hours. \( C_\infty \) is the amount present in mg when \( t \) is infinite and its value equals the amount in mg delivered by a tubocurarine infusion in one hour divided by the constant \( k \). It has already been found that for tubocurarine in the plasma and interstitial fluid \( k=1 \).

From this equation it will be seen why an initial dose at the beginning of this method of tubocurarine administration is essential. If administration is begun by using only the tubocurarine infusion maintenance dose without an initial dose, it will require infinite time to reach
a plasma and interstitial fluid level of tubocurarine sufficient to produce adequate paralysis (fig. 2). Even if the tubocurarine infusion maintenance dose is doubled it will require 42 minutes to produce adequate paralysis.

![Accumulation curves of tubocurarine. No initial dose. Broken line indicates 15 mg dose level necessary for adequate paralysis. Curve OL from a continuous drip of 15 mg/hour requires infinite time to reach adequate level. Curve OMN from a continuous drip of 30 mg/hour requires 42 minutes to reach adequate level at M. By changing the values along the tubocurarine axis these curves are valid for other doses.](image)

**FIG. 2**

Comparison of methods

Gray and Halton (1946), in their original publication, suggest 10–20 mg as the initial dose of tubocurarine. Experience has shown, and this paper has explained, why such an initial dose, although adequate to produce satisfactory paralysis, does not remain effective for more than a few minutes. This has led to the practice of giving a large initial dose, followed by smaller doses as required.

For the purpose of comparison of this method with that described here, let it be assumed that a patient is paralyzed with an initial dose of 45 mg to which is added sufficient 5 mg doses to maintain paralysis. Let us assume also that this patient could have been paralyzed with 15 mg and this paralysis could be maintained by a continuous infusion which delivered 15 mg per hour.

In both cases tubocurarine probably disappears from the plasma and interstitial fluid according to equation (3).

Figure 3 shows that to maintain paralysis for 1 hour the amounts of drug required by the two methods would be 45 mg as compared with 30 mg; for paralysis lasting 2 hours, 60 mg compared with 45 mg, and so on. These differences are even greater when 45 mg is given to a patient in whom paralysis could be obtained with an initial dose of 10 mg and maintained on a 10 mg/hour infusion; for paralysis lasting 1 hour the amounts are 45 mg as compared with 20 mg, and for paralysis lasting 2 hours, 50 mg compared with 30 mg, which means the patient would receive 125 per cent and 66 per cent, respectively, more of the drug than he needed. The method advocated in this paper puts the minimum load on excretion, destruction, and binding sites (Chagas, 1962), which are the mechanisms of the body for tubocurarine clearance. Furthermore, the paralysis produced will be smoother; increased muscle tone with the other method is indicated by the shaded area of the graph in figure 3.

**PLASMA-INTERSTITIAL FLUID EQUILIBRIUM**

By comparing plasma levels of tubocurarine in arterial and venous blood, Cohen, Paulson and Elert (1957) found that equilibrium between plasma and interstitial fluid is established in 10 to 20 minutes.

In a review by Kalow (1959) a compilation has been made from the data published in four papers.
of the initial plasma half-clearance time of tubocurarine, and the average time was 5.7 minutes. Using this time in equation (1) the value of \( k \), for tubocurarine in plasma only, becomes 7.26. On the basis of a plasma volume of 3.5 litres and an interstitial fluid volume of 10.5 litres, we may now calculate the time of equilibrium between the plasma and interstitial fluid. The concentration of tubocurarine in the plasma is \( Ce^{-7.26t} \), and the concentration of tubocurarine in the combined plasma and interstitial fluid is \( Ce^{-t} \).

Equating these fractions and solving for \( t \) will give the time of equilibrium; it is 13.2 minutes and is in agreement with the finding of Cohen, Paulson and Elert (1957).

It will be noted that the time taken for the establishment of equilibrium of tubocurarine between the plasma and interstitial fluid is short, and so may be disregarded without affecting the calculations and graphs from equation (3) when dealing with the combined plasma and interstitial fluid; our results agree in general with other observations (Pelikan et al., 1950; Kalow, 1959; Pittinger, Morris and Cullen, 1951).

Equation (3) may be used to determine at any time, \( t \), after equilibrium, the plasma concentration of tubocurarine following a dose of \( Co \). This value may then be compared with the findings of Pittinger, Morris and Cullen (1951) who used chemical methods to determine plasma tubocurarine concentration. Immediately after the intravenous injection of tubocurarine the plasma concentration approximates the theoretical maximum calculated on the basis of the expected plasma volume (Cohen, Paulson and Elert, 1957; Marsh, 1952), which is \( Ce^{-t} \). The concentration of tubocurarine in the combined plasma and interstitial fluid 20 minutes (0.33 hours) after the injection would be \( Ce^{-0.33t} \); after dividing this fraction by \( Ce^{-t} \), it is found that in 20 minutes the plasma concentration is 18 per cent of the initial concentration. Pittinger, Morris and Cullen (1951) illustrated their findings graphically on six anaesthetized patients given single intravenous injections of tubocurarine. On examination and measurement of their graphs 20 minutes following injection, it appears that the average plasma concentration for five patients was 20 per cent of the initial concentration. At 60 minutes, comparable figures are 9.5 per cent compared with 9.6 per cent.

**CONCENTRATED TUBOCURARINE INFUSION**

It has been shown that the initial dose of drug required to produce paralysis in the anaesthetized patient is between 10 and 20 mg. The optimum initial dose could be arrived at by starting curarization with a concentrated infusion capable of delivering, say, 100 to 150 mg per hour, and by then changing over to a weak maintenance infusion when satisfactory paralysis had been obtained. This is clearly not a practical method for routine use, as overdosage could occur, the use of two different strengths of tubocurarine solutions could lead to accidents, and, as already explained, there would be a considerable delay in the onset of adequate paralysis.

However, by limiting the above concentrated infusion to deliver a safe maximum of, say, 30 mg, the validity of the accumulation and disappearance curves and the equations, (3) and (4), they represent could be confirmed in another way.

Several anaesthetized patients were given 30 mg of tubocurarine by a steady infusion during periods of 11 to 29 minutes. By the feel of the reservoir bag it was easy to judge when the patient became paralyzed, \( t_1 \), and then later when the muscles tightened up, \( t_3 \), from such a dose; the time of these two events after the start of the infusion was recorded. The time taken for the 30 mg to drip in was also recorded, \( t_1 \). In equation (4) we can use \( t_1 \) to calculate the optimum initial dose. The tubocurarine level in the plasma and interstitial fluid continues to rise until \( t_3 \), and its value can be estimated from equation (4). After this, the amount will decrease on a disappearance curve according to equation (3). When it falls to the optimum dose level, time \( t_3 \) can be calculated which is the time when the patient's muscles should tighten up according to these calculations. It is then possible to compare
this time, $t_3$, with the recorded time of $t_3$. In a typical case, 30 mg was given in 17 minutes, and the sequence of events may be followed in figure 4.

![Diagram of tubocurarine infusion](image)

**FIG. 4**
Concentrated tubocurarine infusion of 30 mg delivered in 17 minutes, $t_1$, reached 26 mg at $t_2$ on accumulation curve OJ. The optimum paralyzing dose, determined by the feel of the reservoir bag, occurred in 10 minutes, $t_3$, and was 16 mg. When the level of tubocurarine at J decreased on the disappearance curve JK to the optimum dose of 16 mg, the time when muscle tone would return was indicated on the graph at 46 minutes, $t_4$. The actual recorded time of returning muscle tone, $t_5$, as determined by the feel of the reservoir bag, was 42 minutes.

**DISCUSSION**

The maintenance dose of tubocurarine by continuous infusion is 10 to 20 mg per hour. This finding supports the statement by Burroughs Wellcome (1951) in their pamphlet that “It is estimated that over short periods the body can eliminate about 15 to 20 mg of d-tubocurarine per hour”.

The maintenance dose per hour remained remarkably constant in the majority of cases. In a few patients the infusion rate had to be reduced during the third and fourth hours of curarization, and then by not more than 30 per cent. This finding was anticipated by Mapleson and Mushin (1955) who suggested that “during operations of magnitude, progressive depression of the circulation and of the excretory mechanism may well occur”. However, it is reassuring to note that in the use of tubocurarine in tetanus by the total paralysis regime, the dose requirement per hour in ten patients remained “remarkably constant in individual patients” for periods up to six days (Alhady et al., 1960). In a similar report (Powell, Brimblecombe and Stoneman, 1958), two patients were curarized for two weeks, one needing 440 mg/day; in both cases the “requirements remained fairly constant”, and the patients recovered. Recently Spalding and Crampton Smith (1963) have stated that in severe tetanus an adult requires about 15 mg/hour during treatment lasting two to four weeks.

During controlled ventilation the blood carbon dioxide can be maintained at normal to low levels (Gray and Jackson Rees, 1952), and this results in an increase in blood pH (Dundee, 1952). Recently, it has been shown, in the dog (Utting, 1963), that an increase in blood pH lowers plasma concentrations of tubocurarine and that this may be due to changes in the receptor substance of cell membranes. This finding may explain the slight difference in half-life estimations of tubocurarine between conscious subjects and anaesthetized patients whose respiration is controlled.

Neff, Mayer and Thompson (1950) state that a 50 per cent oxygen-nitrous oxide mixture usually produces first plane anaesthesia; however, recently (Editorial, 1963) it has been pointed out that consciousness might be regained when using gas and oxygen only in this proportion. Any possibility of this may be avoided by using halothane, and Mackay (1957) found that 0.5–1 per cent was sufficient strength for maintenance. An early report (Bryce-Smith and O’Brien, 1956) advised caution when using tubocurarine with halothane. Anaesthetists who have used these drugs together would probably agree with the recent work of Summers, Koons and Denson (1962) who find that the administration of rational doses of tubocurarine during halothane anaesthesia does not produce a significant degree of arterial hypotension.

In the cases reported in this paper pulmonary ventilation was performed manually; recently,
however, a Manley (1961) mechanical ventilator has been used on a number of patients with equally good results.

A gallamine triethiodide infusion was used in a few patients in a manner similar to that already described. The value of k in equation (1) for gallamine triethiodide in the plasma and interstitial fluid was found to be about 1.6. Although satisfactory paralysis was maintained, this drug has the disadvantage of producing tachycardia.

The accumulation curve of tubocurarine represented by equation (4) might be applied in the quantitative assessment of myasthenia gravis. The test dose of tubocurarine in this disorder is between 0.5 and 2 mg. By delivering tubocurarine to the patient at a constant rate of, say, 5 mg/hour, the amount in the combined plasma and interstitial fluid would reach 0.5 mg in 6 minutes, and 2 mg in 30 minutes. In this way the time and threshold at which symptoms appeared could be determined.

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REFERENCES


ADMINISTRATION DE LA TUBOCURARINE BASEE SUR LES COURBES DE DISPARITION ET D'ACCUMULATION CHEZ L'HOMME ANESTHESIE

SOMMAIRE
Description d'une méthode permettant d'obtenir une légère curarisation et une remise rapide par application de quantités minimales de tubocurarine. Après administration d'une dose initiale de 15 mg en général, la paralysie est maintenue par une perfusion continue dont le débit est réglé de manière à fournir par heure une dose correspondant à peu près à la dose initiale. A partir d'une interprétation mathématique de ces phénomènes on peut obtenir une équation de disparition exponentielle de la tubocurarine de l'eau extracellulaire. On utilise la ventilation contrôlée avec une anesthésie superficielle à l'halothane. On ne nécessite pas d'autre injection d'anesthésique ou d'analgésique. La néostigmine permet d'obtenir un réveil prompt et complet. Description de la courbe d'accumulation de la tubocurarine et indication de ses applications. Le temps nécessaire pour atteindre l'équilibre entre le plasma et les liquides interstitiels a été calculé.