TUBOCURARINE AND RENAL FAILURE

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SUMMARY

Different observations concerning the duration of the neuromuscular blocking effect of tubocurarine in patients with renal failure have been rationalized by pharmacokinetic analysis. Computer simulations predict that absence of renal function will have little effect on the duration of action of relatively small single doses of tubocurarine but that the duration of action of large single doses and multiple doses will be prolonged significantly.

It is now generally recognized that renal failure or impaired renal function requires changes in the dosage regimen of many drugs to prevent drug accumulation and toxic effects (Bennett, Singer and Coggins, 1970). A rigorous pharmacokinetic approach for calculating individualized dosage regimens of rapidly distributed drugs for patients with impaired renal function has been presented recently (Dettli, 1970). Considerably more complicated are assessments of the likely effect of renal failure on the elimination kinetics and particularly on the pharmacological effect of drugs with so-called multiple-compartment distribution characteristics. The time course of action of such drugs (of which tubocurarine is one) depends on the site of action of the drug; more specifically, on the apparent body compartment of which the site of action is a part (Gibaldi, Levy and Weintraub, 1971).

It has been shown recently that the kinetics of the neuromuscular blocking effect of tubocurarine in man can be characterized effectively and rigorously on the basis of a three-compartment linear system for tubocurarine distribution and elimination, with the site of action located in the central compartment (Gibaldi, Levy and Hayton, 1972). This permits an assessment of the likely effect of renal failure on the duration of action of tubocurarine under different dosing conditions. Such an assessment is deemed particularly timely and pertinent in view of recent observations on the effect of renal failure on the duration of the neuromuscular blocking effect of tubocurarine. Riordan and Gilbertson (1971) showed unusually prolonged neuromuscular blockade after several doses of tubocurarine while Churchill-Davidson, Way and de Jong (1967) found that the duration of action of this drug was normal in six patients with terminal renal failure. It will be shown that these observations can be rationalized readily on pharmacokinetic grounds. The likely effect of renal failure on the duration of action of tubocurarine has been determined as a function of dose for single doses, and as a function of the number of doses for multiple doses of the drug.

METHODS

All calculations and simulations are based on the pharmacokinetic model for tubocurarine distribution and elimination in normal subjects previously developed on the basis of clinical data (Gibaldi, Levy and Hayton, 1972) and depicted in figure 1. Duration

![Diagram of pharmacokinetic model](image)

Fig. 1. The pharmacokinetic model for tubocurarine distribution and elimination in man developed by Gibaldi, Levy and Hayton (1972). Rate constants, in reciprocal minutes, are shown next to the arrows which represent apparent first-order processes for transfer of drug between compartments, and for metabolism and renal excretion from the central compartment. The simulations of the effect of renal failure, presented in the subsequent figures, are based on this pharmacokinetic model but with the excretion route eliminated by setting the excretion rate constant to zero.
of action was calculated with recovery of 10 per cent of normal twitch force of the adductor muscles of the thumb due to supramaximal ulnar nerve stimulation as the endpoint. It was assumed that renal failure reduces the apparent first-order rate constant for excretion of tubocurarine to zero, but that all other parameters remain normal. The various rate constants which characterize the pharmacokinetic model were used as input data for the determination, by digital computer, of the time course of drug levels in the central compartment of the body following intravenous injection of various doses of tubocurarine. Duration of action is the time during which the amount of drug in the central compartment exceeds or equals the amount required to reduce normal twitch force by 90 per cent (Gibaldi, Levy and Hayton, 1972).

RESULTS AND DISCUSSION
The relationship between intravenous dose of tubocurarine and duration of the neuromuscular blocking effect in normal subjects (Gibaldi, Levy and Hayton, 1972), and the predicted relationship for subjects with renal failure are shown in figure 2. The absence of a renal excretory pathway for tubocurarine increases the duration of action slightly in the low dose range, and considerably at higher doses. For example, the duration of action of a 4 mg/sq.m dose is increased by only 18 per cent while that of a 16 mg/sq.m dose is increased by 68 per cent. The reason for this difference becomes evident upon examining the time course of drug elimination from the central compartment of the body under normal conditions and during renal failure (fig. 3). The initial elimination phase from the central compartment (which includes blood plasma) is largely due to distribution of the drug into the two "tissue" compartments while the subsequent elimination phase reflects mainly the effects of metabolism and excretion. Lack of excretory capability will therefore affect primarily the terminal elimination phase. This has also been shown directly in nephrectomized dogs (Cohen, Corbascio and Fleischli, 1965). The endpoint for 10 per cent recovery, 2.86 mg/sq.m in the central compartment (Gibaldi, Levy and Hayton, 1972), represents 48 per cent of a 6 mg/sq.m dose but only 9.5 per cent of a 30 mg/sq.m dose. Recovery from the neuromuscular blocking effect occurs therefore in the predominantly distributory phase of the low dose, and in the terminal elimination phase of the larger dose.

Walts and Dillon (1968) suggested a tubocurarine dosage regimen of 8 mg/sq.m initially, followed by 2 mg/sq.m maintenance doses upon recovery from the effect of the preceding dose. This regimen elicits a relatively constant duration of effect of approxi-
mately 20 minutes for each dose in normal subjects (fig. 4). Absence of renal excretory function has a relatively small effect on the duration of action of the first dose (33 per cent increase) but causes progressively larger increases in duration so that the effect of the eighth dose lasts 85 per cent longer than in normal subjects (fig. 4).

These results show that renal failure will affect primarily the duration of action of large single doses or multiple doses of tubocurarine. It is therefore quite reasonable that Churchill-Davidson, Way and de Jong (1967) did not notice any readily apparent effect of renal failure on the duration of action of single doses of tubocurarine while Riordan and Gilbertson (1971) observed pronounced prolongation of neuromuscular blockade in a patient who received two 45 mg doses followed by a number of 10 mg maintenance doses. The data presented here are based on average results from normal subjects and on the assumption that renal failure affects only excretory function. Such variables as state of hydration and blood flow, which may affect the response of an individual patient to tubocurarine, were not taken into consideration. Nevertheless, the simulations should be useful not only in explaining previous clinical observations but as an initial guide for determining tubocurarine doses for patients in renal failure, pending subsequent adjustments of the dosage regimen based on the individual patient's response to the first dose.

**Fig. 4.** Predicted duration of effect of successive 2 mg/sq.m maintenance doses of tubocurarine administered after an initial dose of 8 mg/sq.m. The endpoint is recovery of 10 per cent of normal twitch force. ● = normal subjects; ○ = subjects with total renal failure.

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**REFERENCES**


**TUBOCURARINE ET INSUFFISANCE RENALE**

**SOMMAIRE**

En recourant à une analyse pharmacocinétique, on a procédé à la rationalisation de diverses observations relatives à la durée de l'effet bloquant neuromusculaire exercé par la tubocurarine chez des malades atteints d'insuffisance rénale. Des simulations au computer prévoient que l'absence de fonction rénale exercera peu d'effet sur la durée d'action de doses uniques relativement faibles de tubocurarine, mais que la durée d'effet de doses uniques élevées et de doses multiples sera prolongée d'une manière significative.

**TUBOCURARIN UND NIERENVERSAGEN**

**ZUSAMMENFASSUNG**


**TUBOCURARINA E INSUFICIENCIA RENAL**

**RESUMEN**

Diversas observaciones sobre la duración del efecto bloqueante neuromuscular de tubocurarina en pacientes con insuficiencia renal han sido recionalizadas mediante análisis farmacocinético. Simulaciones con computadoras predicen que la ausencia de función renal tendrá poco efecto sobre la duración de la acción de dosis únicas relativamente pequeñas de tubocurarina, pero que la duración de la acción de dosis únicas grandes y dosis múltiples será prolongada significativamente.