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Pharmacokinetics and Pharmacodynamics of Metocurine in Humans with and without Renal Failure

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The pharmacodynamics and pharmacokinetics of metocurine were studied in five neurosurgical patients with normal renal function, and in five anephric patients during and following a renal transplant. Following a single intravenous dose of metocurine (0.3 mg/kg), measurements of serum levels and urinary excretion were made using a specific radioimmunoassay for metocurine. Evoked compound electromyographic (ECEMG) response of the thumb adductor to supramaximal stimulation of the ulnar nerve was also studied. In the patients for renal transplant, plasma clearance of metocurine was significantly reduced (0.38 *vs.* 1.2 ml·kg^{-1}·min^{-1}, $P < 0.01$) and the elimination half-life was significantly prolonged (11.4 *vs.* 6.0 h, $P < 0.01$). The higher serum concentration of metocurine in patients for renal transplant was accounted for by the absence of renal excretion and a reduced total volume of distribution (0.353 *vs.* 0.472 l/kg, $P < 0.05$). The mean serum metocurine concentration necessary for 90 per cent inhibition of the ECEMG was 2.3 times greater in patients undergoing renal transplant than in patients undergoing craniotomy, 1.05 *vs.* 0.46 μg/ml ($P < 0.01$). Although serum metocurine concentrations were still high at the end of the renal transplants, reversal of the neuromuscular blockade was possible. Metocurine appears to be an acceptable neuromuscular blocking agent for patients in renal failure although no major advantage over *d*-tubocurarine and pancuronium could be found. (Key words: Kidney: failure. Neuromuscular relaxants: metocurine. Pharmacokinetics: metocurine.)

HEMODIALYSIS has prolonged the life span of patients in renal failure, and thus has increased their likelihood of undergoing surgery. It is important to known how renal failure affects the pharmacokinetics (drug concentration *vs.* time) and the pharmacodynamics (drug concentration *vs.* biologic effect) of drugs we administer. Neuromuscular blocking agents such as metocurine are often used as an adjunct to anesthesia, and the relatively few cardiovascular effects[1] of metocurine have popularized its use. Studies of pharmacokinetics of metocurine in normal humans showed that 48 per cent of a bolus intravenous dose was excreted unchanged in the urine in 24 h.[2] Therefore, patients in renal failure will undoubtedly have altered pharmacokinetics.

Patients on dialysis may also have altered pharmacodynamics owing to changes in intracellular to extracellular potassium and sodium concentration ratios, calcium concentration, magnesium concentration, neurotransmitter receptor availability and number, and protein binding of metocurine. This study quantitates the altered pharmacodynamics and pharmacokinetics of metocurine in patients with renal failure.

Methods

Five patients scheduled for craniotomy and five patients scheduled for renal transplant were studied. Informed consent was obtained and the study was approved by the Institutional Review Board of Columbia University. Patients undergoing craniotomy had a mean age of 40 ± 7.0 yr (mean ± SE), and serum electrolytes, hemoglobin, and creatinine within normal limits. Patients for renal transplant had a mean age of 31 ± 6.5 yr, serum electrolytes within normal limits, and a mean hemoglobin of 8.0 ± 0.9 g/dl. Their mean serum creatinine concentration was 10.6 ± 1.7 mg/dl, even though they had undergone hemodialysis to their dry weight within 24 h of operation.

All patients for craniotomy were premedicated with a barbiturate and atropine intramuscularly, and they received oxacillin and dexamethasone intravenously during surgery. All patients for renal transplant received a narcotic and atropine intramuscularly and hydrocortisone, 200 mg, iv as premedication. Anesthesia was induced with thiopental, and tracheal intubation was facilitated with succinylcholine. Anesthesia was maintained with halothane 0.5–1.0 per cent and nitrous oxide 50–70 per cent, inspired. Mechanical ventilation maintained moderate hyperventilation (Pa_{CO_2}, 25–35 torr), and esophageal temperatures were maintained at 34.5–36.0° C in all patients. Neuromuscular transmission was assessed by quantitating the compound electromyographic twitch height of the adductor of the thumb in response to

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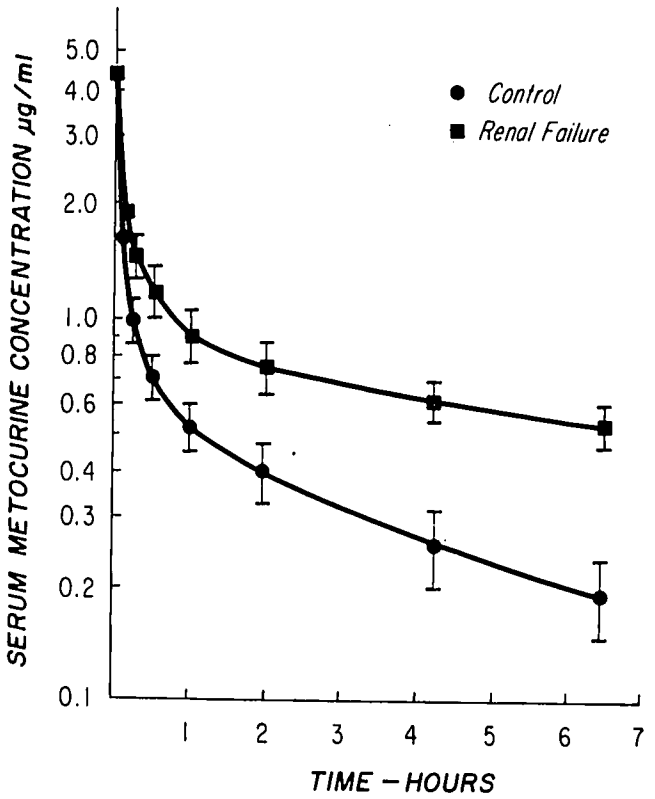

FIG. 1. Serum decay curves for metocurine (mean ± SE) in controls (n = 5) and in patients in renal failure (n =5).

supramaximal stimulation of the ulnar nerve from a Grass S8 stimulator. Responses to single stimuli of 0.2-ms duration delivered at a frequency of 0.1 Hz (6/min) were recorded.

After succinylcholine administration, return of twitch height to normal was assessed by train-of-four stimulation and then 15 min were allowed to elapse before a single intravenous dose of 0.3 mg/kg metocurine was rapidly injected within 4 s. Blood samples were drawn from a contralateral arterial line at 1, 2, 4, 8, 16, 32, 64, 90, 128, 180, 256, and 360 min. A 24-h serum sample was obtained by venipuncture. Twenty-four hour urine collections were obtained from all patients. Plasma and urine samples were analyzed for metocurine concentration by a modification of the radioimmunoassay of Horowitz and Spector for *d*-tubocurarine (*d*Tc).[3] The modification consisted of using metocurine as the standard at ten times the concentration used for *d*Tc and increasing the incubation time to 48 h. The concentration of metocurine which inhibits antigen-antibody binding by 50 per cent is 2.5 ng/ml. The maximum variation of the assay is ±5 per cent at all concentrations. At the end of the procedure, 2.5–5.0 mg neostigmine and 1.0–1.5 mg atropine were given to antagonize the effects of metocurine. No additional drugs were administered intraoperatively.

Comparison between patients with and without renal failure was made by applying Student's *t* test for unpaired data. The method of Wagner[4] was used to analyze the pharmacokinetic parameters. This method assumes that the general kinetic model is an n-compartment mammillary system with elimination only from the central compartment. For individual patients, data of serum concentration of drugs *vs.* time are fitted to the required number of exponential terms using log-linear regression analysis. The multiple terms of the equation were determined by the peeling (or stripping) method, each term having three or more points. The plasma clearance (Cl_p), half-life of elimination ($t_{1/2}$), initial volume of distribution (V_1), total volume of distribution (VD_{area}), and intercompartmental rate constants were calculated from the coefficients and exponents of the derived polyexponential equation. The method for calculating Cl_p, $t_{1/2}$, V_1, and VD_{area} has been described by Wagner.[5] The method for calculating the intercompartmental rate constants has been described by Gibaldi and Perrier.[6]

Results

For each plasma decay curve, a triexponential function gave the best fit with the experimental data. The equation describing the pharmacokinetics of the mean serum concentrations of metocurine as a fraction of the dose in the central compartment for the five normal patients was:

$$Q_1/D = 0.087e^{-0.002t} + 0.189e^{-0.042t} + 0.831e^{-0.42t}$$

TABLE 1. Pharmacokinetic Characteristics of Metocurine in Humans with and without Renal Failure (mean ± SE)

	Renal Failure (n = 5)	Normal (n = 5)
$t_{1/2}$ Elimination (h)	11.4 ± 1.5*	6.0 ± 0.95
Cl_p (ml·kg^{-1}·min^{-1})	0.38 ± 0.06*	1.20 ± 0.30
V_p (l/kg)	0.058 ± 0.011	0.053 ± 0.005
VD_{area} (l/kg)	0.353 ± 0.053†	0.472 ± 0.055
k_{12}	0.245 ± 0.063/min	0.189 ± 0.024/min
k_{21}	0.183 ± 0.031/min†	0.117 ± 0.025/min
k_{13}	0.058 ± 0.009/min	0.067 ± 0.012/min
k_{31}	0.015 ± 0.003/min	0.011 ± 0.001/min
k_{10}	0.007 ± 0.001/min†	0.024 ± 0.008/min

$t_{1/2}$ elimination = half-life of the third component of the plasma decay curves; Cl_p = plasma clearance; V_p = apparent volume of distribution of the central compartment; VD_{area} = total apparent volume of distribution; k_{12}, k_{21}, k_{13}, k_{31} = rate constants for bidirectional transport of drug between compartments 1 and 2, and 1 and 3, indicating the fraction of the drug transferred from a certain compartment to another in one min. k_{10} = rate constant for elimination from the central compartment.

* Significantly different, $P < 0.01$.

† Significantly different, $P < 0.05$.

and that for the patients with renal failure was:

$$Q_1/D = 0.160e^{-0.0011t} + 0.232e^{-0.036t} + 0.773e^{-0.49t}$$

where Q_1 is the amount of the drug in the central compartment, D is the dose, and t is the time in min. Differences between the two plasma decay curves became significant at 16 min ($P < 0.05$) (fig. 1). Table 1 summarizes the pharmacokinetic parameters.

Four of five patients in renal failure had a 24-h urinary excretion of metocurine less than 3 per cent of the total dose injected. The transplanted kidney of one patient excreted 46 per cent of the total dose in 24 h, and therefore data obtained after anastomosis of the renal artery at 4 h was excluded from his serum decay curve. Table 2 summarizes the various routes of elimination of metocurine. Estimated biliary excretion in normal patients was taken from the work of Meijer *et al.*[2] This may be an underestimation, as bile was collected by means of a "t" tube in this experiment. Biliary excretion in patients with renal failure was calculated by assuming that the biliary elimination rate constant was the same as in normal patients. This resulted in a higher postulated biliary excretion of metocurine because of the higher plasma level of metocurine in patients who underwent renal transplant.

In patients with renal failure, a return to 10 per cent of control of the ECEMG response occurred at a serum metocurine concentration of 1.05 ± 0.26 μg/ml (mean ± SE), while in normal patients the return to 10 per cent of control was recorded at a serum concentration of 0.46 ± 0.11 μg/ml. This difference is significant ($P < 0.01$).

Discussion

This study analyzed the pharmacokinetics of metocurine according to an open three-compartment model. According to this model, the elimination of metocurine is 99 per cent complete at 24 h for normal humans, yet renal excretion accounts for only 43 per cent of the dose. Biliary excretion has been shown to be less than 2 per cent in normal patients and no metabolites of metocurine have been found.[2] This leaves 55 per cent of the dose unaccounted for. The most likely explanation is that there is a tissue depot for metocurine. Matteo *et al.* have postulated a deep tissue depot to explain the elimination of (*d*Tc).[7] We have also found significant quantities of *d*Tc in tissue of rats eight days after a single dose of 0.3 mg/kg (unpublished data). Essential to the three-compartment model is that this tissue depot of *d*Tc be considered a route of elimination with its own specific rate constant. Gibaldi *et al.* postulated this same model for *d*Tc and calculated the rate constant for "nonrecoverable" elimination.[8] This point is important because, although all the metocurine is not excreted from the body, it is totally eliminated from the plasma. Thus, nonrecoverable elimination is a major route of elimination, greater than urinary excretion.

By using the intercompartmental rate constants from the normal patients' plasma decay curve and assuming a renal excretion of zero per cent, a postulated plasma decay curve for patients in renal

TABLE 2. Routes of Elimination of Metocurine in Humans with and without Renal Failure (mean ± SE)

	Renal Failure (n = 4)	Normal (n = 5)
Per cent of dose in 3 compartments at 24 h	22 ± 4.4	0.05 ± 0.02
Per cent of dose excreted in urine at 24 h	<3	43 ± 3
Per cent of dose excreted in bile at 24 h*	7 ± 1.4	2 ± 0.4
Per cent of dose eliminated by unaccountable means	~68	~55

* From Reference 2. See text.

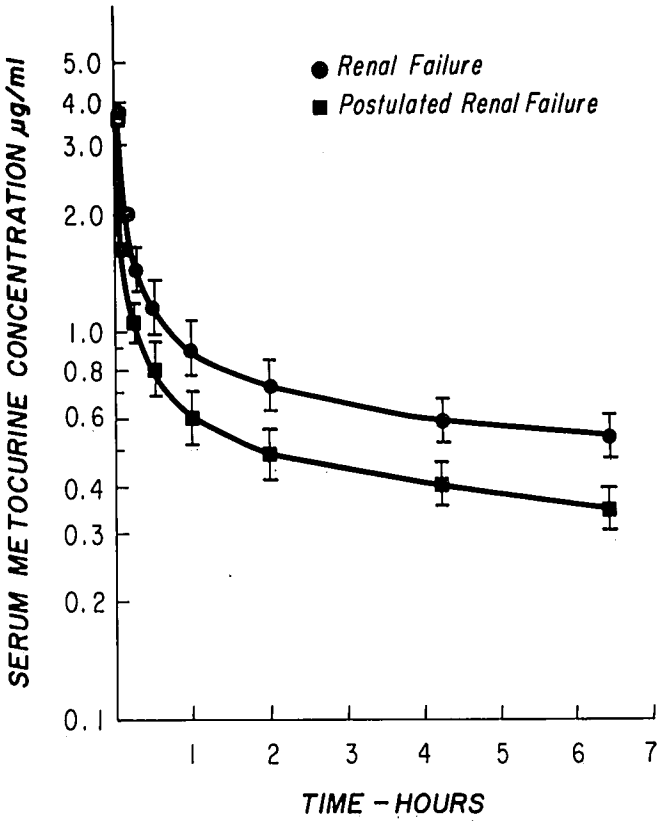

FIG. 2. Serum decay curve for metocurine (mean ± SE) in patients in renal failure (n = 5) and in normal patients whose renal elimination has been adjusted to zero (n = 5).

failure was calculated by the method described by Wagner (fig. 2):

$$Q_t/D = 0.100e^{-0.0012t} + 0.170e^{-0.040t} + 0.823e^{-0.412t}$$

This line underestimates the measured serum metocurine concentration of patients in renal failure. The reason for this is that the total volume of distribution is less in patients with renal failure (0.353 *vs.* 0.472 l/kg). Buzello and Agoston[9] also found a decreased total volume of distribution in anuric patients receiving pancuronium, 14 l *vs.* 21 l, yet McLeod *et al.*[10] found an increased volume of distribution, and Somogyi *et al.*[11] found no change. Reasons for these discrepancies may be due to the state of hydration of the patients, and if hemodialysis was chronically performed on them. All our patients received chronic hemodialysis and were dialyzed to their "dry weight" within 24 h of operation. "Dry weight" is an empirical term which signifies the minimum weight a patient has achieved on dialysis without causing vascular instability.

The fact that four out of five of the patients for renal transplant excreted less than 3 per cent of the dose of metocurine is easily explained by the fact that their transplanted kidneys were not functioning post-transplant. The one recipient who did not go into acute tubular necrosis had a 24-h urinary excretion of 46 per cent of the dose and thus proves that a functioning transplanted kidney can excrete metocurine normally.

Finally, we found that to achieve 90 per cent blockade of the thumb adductor in patients with renal failure requires a higher serum metocurine concentration (1.05 μg/ml *vs.* 0.46 μg/ml). The patients for craniotomy were anesthetized for a long enough time to determine a linear relationship for metocurine concentration *vs.* twitch height. Yet the patients for renal transplant did not have enough return of twitch before reversal to determine the same linear relationship. Therefore, 90 per cent blockade of twitch *vs.* serum metocurine concentration was used as an assessment of pharmacodynamics. This degree of paralysis occurred at 30 min in the β phase. Since the neuromuscular junction is considered to be in the central compartment, there should be no disequilibrium between metocurine concentration in the serum and at the neuromuscular junction in the β phase.

The increased dose needed for paralysis with metocurine gives it no specific advantage over pancuronium or *d*Tc in patients with renal failure. A prolonged duration of paralysis and a decreased rate of return of twitch similar to that found by Miller *et al.* for *d*Tc[12] and that found by Buzello *et al.* for pancuronium[9] is expected due to the prolonged elevation of serum metocurine concentrations in renal failure. Of significance is the variability of the individual plasma decay curves and degree of paralysis for equal serum metocurine concentrations. Although this variability is no more severe than in normal patients, its consequences are. The patient in renal failure who is overdosed by a moderate dose of muscle relaxant can expect a much longer prolongation of paralysis than a normal patient. In our study, one patient in renal failure was well relaxed (>90 per cent twitch inhibition) for six hours, while another patient in renal failure was well relaxed (>90 per cent twitch inhibition) for only 10 min. This variability makes it imperative to monitor patients in renal failure to insure adequate relaxation without overdosage.

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