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Title : Pharmacokinetics of Metocurine in Man with Renal Failure

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Introduction. The pharmacokinetics of metocurine in man with normal renal function has been documented.[1] Disposition of metocurine in patients in renal failure has not, however, been studied. This study was designed to quantitate the disposition of metocurine in these patients. Neuromuscular blockade in relation to serum metocurine concentration was also studied.

Methods. Five patients scheduled for craniotomy and five patients scheduled for renal transplants were studied after obtaining informed consent. Patients undergoing craniotomy had normal renal function, electrolytes, creatinine and hemoglobin. Patients for renal transplant had a mean age of 31, normal electrolytes, an average hematocrit of 24 percent and an average serum creatinine of 10.6. Anesthesia was induced with thiopental, and tracheal intubation was facilitated with succinylcholine. Anesthesia was maintained with halothane 0.5-1.0% and nitrous oxide 70%. Neuromuscular transmission was assessed by quantitating the electromyographic twitch height of the adductor of the thumb in response to supramaximal stimulation of the ulnar nerve. Responses to single stimuli of 0.2 msec 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 stimulations, and then a single iv dose of metocurine (0.3 mg/kg) was injected. Blood samples were drawn at intervals from a contralateral intraarterial line to be analyzed for metocurine concentration by radioimmunoassay. At the termination of the surgical procedure, neostigmine 2.5 - 5 mg was given iv to antagonize the effects of metocurine. The pharmacokinetic data were analyzed by a three-compartment model and the statistical method of "stripping." "Nonrecoverable metocurine" was calculated by subtracting urinary excretion, estimated biliary excretion, and calculated amount of drug in the three compartments from total dose of metocurine injected.

Results. Patients in renal failure showed a significantly prolonged elimination half-life compared to control patients (10.67 vs 5.25 hrs) and a decreased plasma clearance (0.37 vs 1.13 ml/kg/min). Differences between serum metocurine concentrations in normal versus patients with renal failure became significant at 60 min ($P < .05$)(Fig 1). In patients with renal failure, ECEMG began to return at an average metocurine concentration of 1.22 μg/ml, whereas in patients with normal renal function, neuromuscular transmission returned at a much lower metocurine concentration, 0.52 μg/ml.

Discussion. It is not surprising that patients in renal failure do not eliminate metocurine to the same extent as patients with normal renal function. Four out of five of the renal transplant patients had acute tubular necrosis (ATN). These patients excreted less than 3 percent of administered metocurine in 24 hrs, compared with 42 percent in normal patients. The one patient who did not have ATN excreted 46 percent of the injected dose in 24 hrs, showing that a transplanted kidney can excrete metocurine normally. In normal man, urinary excretion is the prime route of elimination of metocurine (42 percent), and biliary excretion is of minor importance (2 percent).[2] In normal patients this leaves 53 percent of the dose being disposed by so-called "nonrecoverable elimination" at 24 hrs. This nonrecoverable elimination is of even greater significance in patients with renal failure. In these patients, nonrecoverable elimination at 24 hrs may amount to 73 percent of the total dose of metocurine. Nonrecoverable elimination most likely reflects binding of metocurine in the body at nonreactive sites followed by very slow elimination. Matteo et al have shown in man that d-tubocurarine (dTc) is localized in a deep compartment and is very slowly excreted.[3] Matteo has also shown that although metocurine cannot be detected in the serum of man for more than 48 hrs, it can be detected in the urine at 96 hrs.[1] This again suggests a tissue depot and very slow excretion. Furthermore, in rats, significant quantities of dTc have been found in the tissues 8 days after a single injection of 0.3 mg/kg (unpublished data).

The basis for the observation that neuromuscular transmission in patients in renal failure starts to return at serum concentrations 2.3 times greater than those of patients with normal renal function is unclear. Tissue binding of large quantities of metocurine together with an increased requirement of the drug to achieve complete paralysis explains why it has been possible to reverse the effects of a single large dose of metocurine (0.3 mg/kg) with neostigmine without subsequent difficulties.

References

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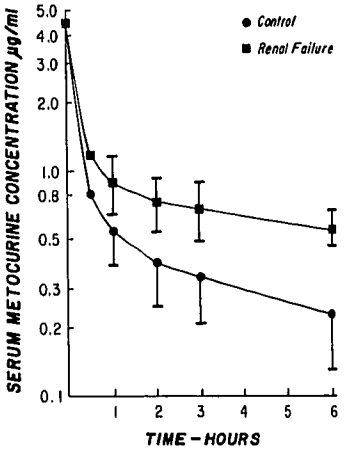

Fig 1. Serum decay curve for metocurine (mean ± SD) in control and patients in renal failure.