Renal Function and the Pharmacokinetics of Neostigmine in Anesthetized Man

Roy Cronnelly, M.D., Ph.D.,* Donald R. Stanski, M.D.,† Ronald D. Miller, M.D.,‡
Lewis B. Sheiner, M.D.,§ Yung J. Sohn, M.D.¶

The pharmacokinetics of neostigmine in patients with normal renal function (n = 8) were determined and compared with those of patients undergoing renal transplantation (n = 6) or bilateral nephrectomy (n = 4). All patients were anesthetized with nitrous oxide and halothane. d-Tubocurarine was infused at a rate sufficient to maintain 90 per cent depression of twitch tension. Ten to 15 minutes prior to the end of operation and anesthesia, the d-tubocurarine infusion was terminated and neostigmine, 0.07 mg/kg, and atropine, 0.03 mg/kg, were given by infusion over a 2-min period. Concentrations of neostigmine in blood drawn periodically during the following four hours were determined by gas–liquid chromatography and the data fitted to a two-compartment pharmacokinetic model. In anephric patients elimination half-life (181 ± 54 min, mean ± SD) was significantly prolonged when compared with comparable values for patients with normal renal function (80 ± 48 min). Total serum clearance was significantly decreased from 16.7 ± 5.4 ml/kg/min in patients with normal renal function to 7.8 ± 2.6 ml/kg/min in anephric patients. Neostigmine pharmacokinetics following renal transplantation were not different from those in patients with normal renal function. It is concluded that renal excretion accounts for 50 per cent of neostigmine clearance and, in the absence of renal function, the serum half-life of neostigmine is prolonged, similar to that of d-tubocurarine. (Key words: Antagonists, neuromuscular relaxants: neostigmine. Kidney: failure; function; transplantation. Neuromuscular relaxants: d-tubocurarine. Pharmacokinetics: distribution; kinetics; models.)

IMPAIRED RENAL FUNCTION has been demonstrated to decrease plasma clearance and increase the duration of action of nondepolarizing muscle relaxants in anesthetized patients.[1,2] Likewise, problems of prolonged neuromuscular blockade or inadequate antagonism have been reported to occur in patients with renal failure.[3,4] We wondered whether these problems might be related to the normal excretion of neostig-

mine and the delayed excretion of the nondepolarizing relaxants. Accordingly, this study was designed to define the pharmacokinetics of neostigmine in anesthetized patients with and without renal function. We also determined the influence of renal transplantation on the pharmacokinetics of neostigmine.

Methods

Eighteen surgical patients were studied after informed consent to participate in the study, approved by the local committee on human experimentation. Eight patients (23–52 years old) had normal renal function as evidenced by normal values for blood urea nitrogen (BUN) and creatinine. Four patients (38–45 years old) were undergoing bilateral or transplant nephrectomy, and six patients (29–44 years old) were undergoing renal transplantation. Transplantation from living related donors had been completed for at least one hour prior to neostigmine administration. All patients were premedicated with diazepam, 10 mg, orally.

Anesthesia was induced with thiopental, 2–4 mg/kg, and maintained with nitrous oxide, 60 per cent, and halothane, 0.4 to 0.5 per cent, end-tidal. Endotracheal intubation was accomplished without the use of other drugs. Supramaximal square-wave bipolar pulses of 0.15-msec duration at 0.15 Hz were delivered to the ulnar nerve at the wrist through 27-g needle electrodes. The resultant force of thumb adduction was quantified with a Grass FT10 force-displacement transducer and recorded on a polygraph. Controlled ventilation kept Pa_{CO_2} between 35 and 40 torr. Esophageal temperature was maintained between 34.5 and 36 C. d-Tubocurarine was administered as an intravenous bolus and then infused at a rate sufficient to maintain 90 per cent depression of twitch tension. Ten to 15 min prior to the end of operation and anesthesia, the d-tubocurarine infusion was terminated and neuromuscular blockade antagonized by neostigmine, 0.07 mg/kg, combined with atropine, 0.03 mg/kg, administered intravenously over a 2-min period by use of an infusion pump. Venous blood was withdrawn from the contralateral arm 0, 2, 4, 6,8, 10, 15, 20, 25, 30, 45, 60, 90, 120, 150, 180, 210 and 240 min following neostigmine administration. Serum was then stored at −35 C until assayed for neostig-

mine. Neostigmine was extracted from serum and concentrations determined by the technique of Chan et al.[5] Samples were assayed with a Varian 2400 gas–liquid chromatograph equipped with an alkali flame ionization detector. Modifications of the technique included a 2-meter coiled glass column, ¼ inch OD, packed with 3 per cent SP2250 in 100/120 Supelcoport® and silanized with hexamethyldisilazane prior to use. Gas flow rates (ml/min) were: nitrogen (carrier) 26, hydrogen 38, and air 200. Temperatures (C) were set at: injector 300, oven 225, and detector 265. Serum containing neostigmine in concentrations ranging from 15 to 300 ng/ml was prepared with pyridostigmine as the internal standard. This method was not used to measure neostigmine concentrations in urine because the extraction process removes many nitrogen-containing compounds in addition to the test drugs, making detection impossible because of interfering substances.

Serum concentration data were analyzed with weighted nonlinear least-squares regression analysis.[6] Data appropriately corrected for the infusion period
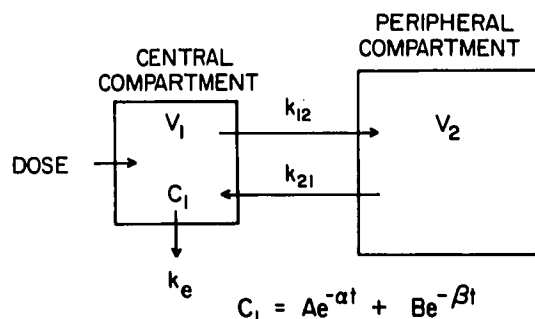

Fig. 1. Diagrammatic representation of the two-compartment pharmacokinetic model used for data analysis of neostigmine. V_1 and V_2 represent apparent volumes of the central and peripheral compartments. k_{12} and k_{21} are first-order rate constants of drug transfer between compartments. k_e is the first-order rate constant for drug elimination from the central compartment. Also shown is the biexponential equation that characterized the model.

were fitted to a two-compartment mamillary (or open) model (fig. 1). This was chosen over a three-compartment model on the basis of statistical evaluation by the methods of Boxenbaum et al.[7] The following

Fig. 2. Examples of the quality of characterization of individual patient data by the pharmacokinetic model. Each figure represents data from one patient. In the upper left figure, the data are from a patient with normal renal function. In the upper right figure, data are from a patient with a newly transplanted kidney. In the lower figure, the data are from an anephric patient. Solid lines represent the fitted function.
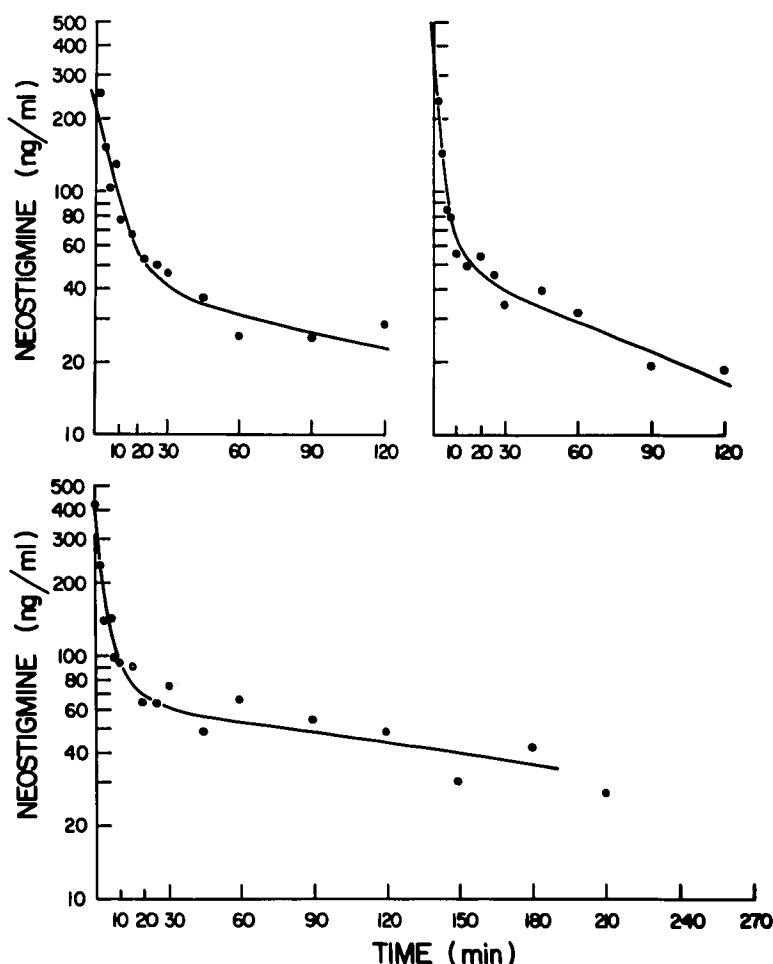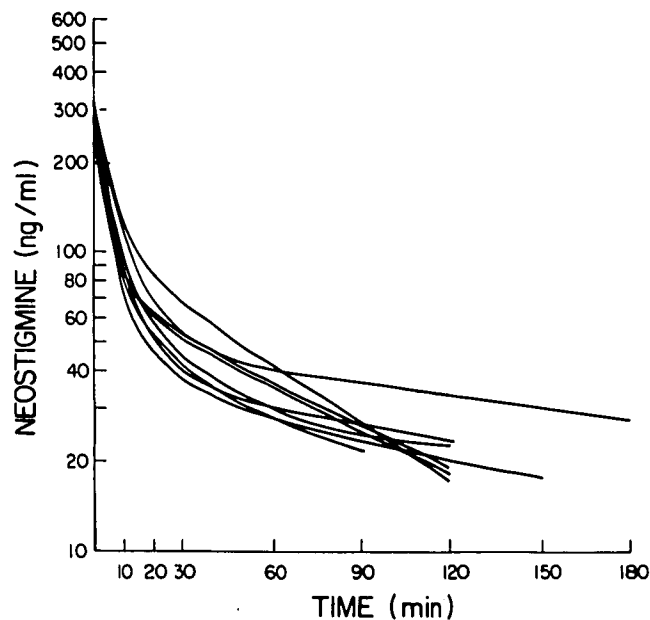
FIG. 3. Disappearance of neostigmine (0.07 mg/kg) from serum following 2-min intravenous infusion in eight patients with normal renal function. Solid lines represent fitted functions. The lengths of the individual lines indicate the times at which serum levels of neostigmine were no longer detectable.

pharmacokinetic parameters were calculated: distribution half-life ($t\alpha_{1/2}$), elimination half-life ($t\beta_{1/2}$), volume of the central compartment (V_1), volume of distribution at steady state ($V_{D_{ss}}$) and total serum clearance (C_1).[6] Comparisons were made using a Student t test for unpaired data. $P < 0.05$ was chosen as the level of significance.

Results

Three examples of the quality of characterization of patient data by the two-compartment model are shown in figure 2. Similar approximations of data points by the fitted functions were obtained for patients in all groups studied.

When administered as a 2-min infusion, initial concentrations of neostigmine ranged from 200 to 350 ng/ml in sera of patients with normal renal function. After one to two hours, serum levels had declined to 15–30 ng/ml. In the majority of patients neostigmine was not detectable after two hours.

Neostigmine pharmacokinetics were not significantly different in patients with normal renal function (fig. 3) and those undergoing renal transplantation (fig. 4 and table 1). In contrast, anephric patients (fig. 5) had a significantly prolonged elimination half-life and decreased total serum clearance of neostigmine when compared with patients with normal renal function or those undergoing renal transplantation (table 1).

Discussion

In the absence of renal function, a significantly decreased plasma clearance and prolonged elimination half-life have been found for both d-tubocurarine and pancuronium.[1,2] Data from the present study indicate a similar significant change of neostigmine pharmacokinetics in patients with absent renal function.

Throughout the present study, a 2-min infusion technique of drug administration was chosen over the clinically used bolus injection to allow better characterization of the distribution phase. In normal, anephric and transplant patients neostigmine distribution was rapid, and half-lives were similar. More rapid mixing and therefore a shorter distribution half-life might have been expected in patients in renal failure, who usually have increased cardiac output values in compensation for anemia, but this was not found (table 1).

The large V_1 (25 l/70 kg) and $V_{D_{ss}}$ (98 l/70 kg) relative to plasma and extracellular volumes were not expected for neostigmine, since it is a quaternary amine and should not easily cross lipid membranes. These data suggest to us that rapid equilibration of neostigmine with tissues comprising both central and peripheral compartments must occur. Also, extensive tissue localization of neostigmine presumably occurred,
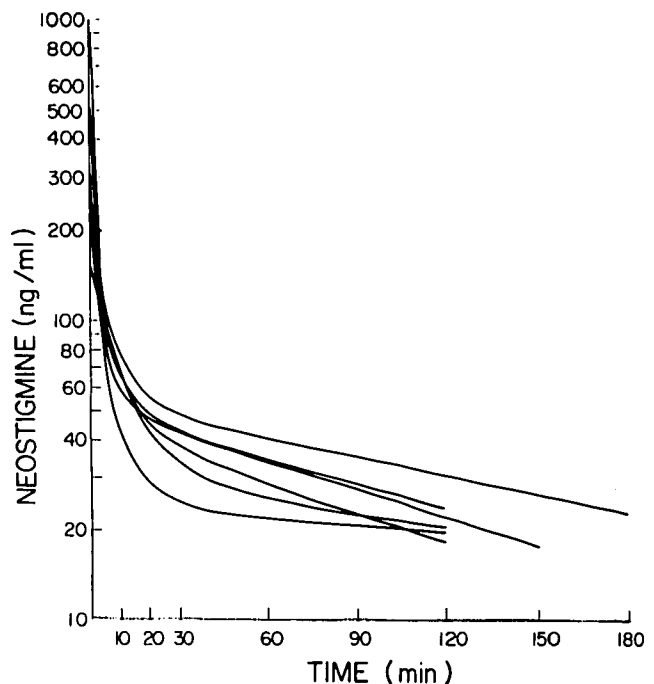

FIG. 4. Disappearance of neostigmine (0.07 mg/kg) from serum following 2-min intravenous infusion in six patients immediately following renal transplantation. Solid lines represent the fitted functions. The lengths of solid lines represent times at which serum levels of neostigmine were no longer detectable.

FIG. 5. Disappearance of neostigmine (0.07 mg/kg) from serum following 2-min intravenous infusion in anephric patients (n = 4). Solid lines represent fitted functions. The lengths of solid lines represent times at which serum levels of neostigmine were no longer detectable.
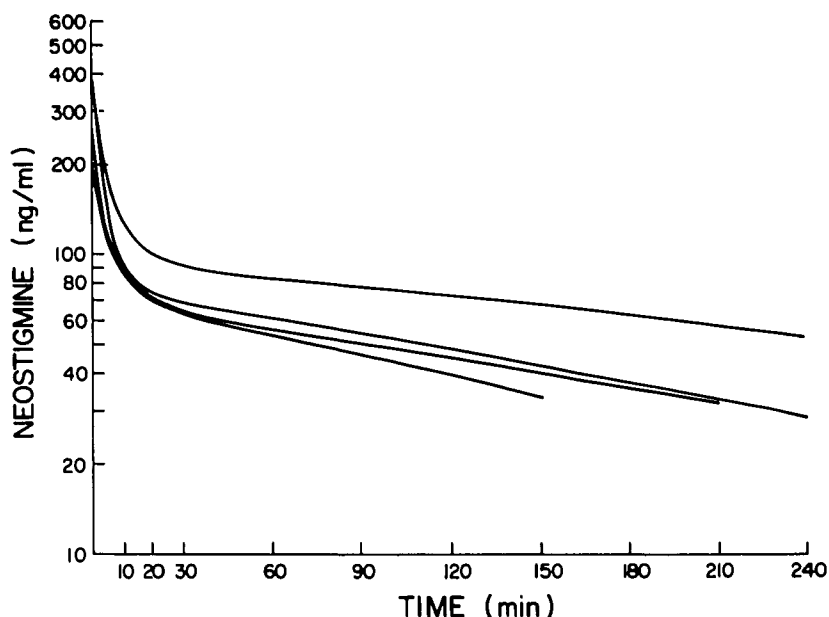
which resulted in enlargment of V_1 and $V_{D_{ss}}$. Renal failure, with a low hematocrit and larger plasma volume, does not appear to alter these distribution volumes significantly.

Plasma clearances of neostigmine are 16.7 ± 5.4 ml/kg/min in normal patients and 7.8 ± 2.6 ml/kg/min in patients without renal function. Thus, approximately 50 per cent (8.9/16.7) of plasma clearance of neostigmine appears to be dependent on renal excretion, and the remainder on nonrenal mechanisms. Nowell et al.[8] found 67 per cent of neostigmine excreted unchanged in urine, following intramuscular administration to unanesthetized patients with myasthenia gravis. If renal excretion occurred solely by glomerular filtration, renal clearance of 1–2 ml/kg/min would be expected.[9,10] Higher values (such as our 8.9 ml/kg/min) suggest a tubular secretory process in addition to glomerular filtration. Roberts et al.[11] found active tubular secretion of ^{14}C-neostigmine in rats and hens, which was blocked by cyanine 863, a known inhibitor of the cationic transport system.

Hydrolysis of neostigmine by cholinesterase could contribute to nonrenal clearance. The amount of neostigmine cleared by this mechanism would be difficult to estimate, although the rate of destruction is slow in vitro, suggesting a minimal contribution.[12,13] Hepatic uptake and metabolism are other possible mechanisms for nonrenal clearance. Considerable evidence for hepatic metabolism and biliary excretion has been found in the rat; however, the existence of similar pathways in man has not been demonstrated.[14–16]

We and Miller et al.[2] found that a newly transplanted kidney is capable of excreting neostigmine and d-tubo-

curarine, respectively, at rates similar to rates of excretion by two normal kidneys. In our study, no acute sign of rejection was evident. We assume that when signs of rejection occur, the ability of the new kidney to excrete neostigmine and d-tubocurarine will be compromised.

We did not correlate blood levels with antagonism because neostigmine was given at the end of operation and anesthesia. At this time, neuromuscular blockade from d-tubocurarine was decreasing, not only because of antagonism by neostigmine, but probably also because of decreasing concentrations of d-tubocurarine and halothane in blood. To correlate blood levels of neostigmine with antagonism would not be an accurate correlation because there are so many factors influencing reversal of neuromuscular blockade. In anesthetized man, the absence of renal function prolonged the elimination half-life of neo-

TABLE 1. Pharmacokinetics of Neostigmine in Patients with Normal or Absent (Anephric) Renal Function and Those with Newly Transplanted Kidneys

	$t\alpha_{1/2}$ (Min)	$t\beta_{1/2}$ (Min)	V_1 (l/kg)	$V_{D_{ss}}$ (l/kg)	C_1 (ml/kg/min)
Normal (n = 8)					
Mean	3.5	79.8	0.37	1.4	16.7
SD	1.1	48.6	0.07	0.5	5.4
Anephric (n = 4)					
Mean	2.5	181.1*	0.42	1.6	7.8*
SD	0.4	54.4	0.1	0.2	2.6
Transplant (n = 6)					
Mean	2.4	104.7	0.37	2.1	18.8
SD	1.3	64.0	0.26	1.0	5.8

* $P < 0.05$.

stigmine, similar to that of *d*-tubocurarine.[2] If we assume that serum concentrations of neostigmine are related to magnitude of antagonism, then recurarization in patients with absent renal function seems unlikely.

References

1. Somogyi AA, Shanks CA, Triggs EJ: The effect of renal failure on the disposition and neuromuscular blocking action of pancuronium bromide. Eur J Clin Pharmacol 12:23–29, 1977

2. Miller RD, Matteo RS, Benet LZ, et al: The pharmacokinetics of *d*-tubocurarine in man with and without renal failure. J Pharmacol Exp Ther 202:1–7, 1977

3. Miller RD, Cullen DJ: Renal failure and postoperative respiratory failure: Recurarization. Br J Anaesth 48:253–256, 1976

4. Miller RD, Stevens WC, Way WL: The effect of renal failure and hyperkalemia on the duration of pancuronium neuromuscular blockade. Anesth Analg (Cleve) 52:661–666, 1973

5. Chan K, Williams NE, Baty JD, et al: A quantitative gas liquid chromatographic method for the determination of neostig-

6. Metzler CM: NONLIN. The Upjohn Co., Kalamazoo, Michigan, 1969

7. Boxenbaum H, Riegelman S, Elashoff R: Statistical estimation in pharmacokinetics. J Pharmacokinet Biopharm 2:123–148, 1974

8. Nowell PT, Scott CA, Wilson A: Determination of neostigmine and pyridostigmine in the urine of patients with myasthenia gravis. Br J Pharmacol 18:617–624, 1962

9. Melman KL, Monelle HF: Clinical Pharmacology. Second edition. New York, Macmillan, 1978, pp 46–49

10. Duchin KL, Schrier RW: Inter-relationship between renal hemodynamics, drug kinetics and drug action. Clin Pharmacokinetics 3:58–71, 1978

11. Roberts JB, Thomas BH, Wilson A: Distribution and excretion of ^{14}C-neostigmine in rat and hen. Br J Pharmacol Chemother 25:234–242, 1965

12. Koelle GB: Anticholinesterase agents, The Pharmacologic Basis of Therapeutics. Fifth edition. Edited by LS Goodman, A Gilman. New York, Macmillan, 1975, pp 454–456

13. Nowel PT, Scott CA, Wilson A: Hydrolysis of neostigmine by plasma cholinesterase. Br J Pharmacol Chemother 19:498–502, 1962

14. Roberts, JB, Thomas BH, Wilson A: Metabolism of ^{14}C-neostigmine in the rat. Br J Pharmacol 25:763–770, 1965

15. Roberts JB, Thomas BH, Wilson A: Excretion and metabolism of oral ^{14}C-neostigmine in the rat. Biochem Pharmacol 15:71–75, 1966

16. Calvey TN: The biliary excretion of neostigmine in the rat. Br J Pharmacol Chemother 28:348–359, 1966