PHARMACOKINETICS OF ATRACURIUM AND OTHER NON-DEPOLARIZING NEUROMUSCULAR BLOCKING AGENTS IN NORMAL PATIENTS AND THOSE WITH RENAL OR HEPATIC DYSFUNCTION

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Before the introduction of atracurium and vecuronium, all the clinically available non-depolarizing neuromuscular blocking agents had a similar pharmacokinetic profile, and were heavily dependent on the kidney for their elimination (Miller and Savarese, 1981). Both atracurium and vecuronium are not significantly dependent on the kidney for elimination of the unchanged drug. In fact, because of Hofmann elimination and ester hydrolysis, theoretically, atracurium should not be dependent on either the kidney or liver for its elimination. Since 1981, atracurium has been studied in patients with impaired renal or hepatic function, or both. These data will be evaluated in relationship to those concerning other non-depolarizing neuromuscular blocking agents.

PHARMACOKINETICS IN PATIENTS WITH NORMAL RENAL AND HEPATIC FUNCTION

Atracurium has an elimination half-life of less than 30 min (Ward et al., 1983; Fahey et al., 1984), while the elimination half-life of vecuronium is about 60–70 min (Cronnelly et al., 1984). All other non-depolarizing neuromuscular blocking agents have elimination half-lives greater than 90 min (Miller and Savarese, 1981). Despite the difference in elimination half-lives, the duration of neuromuscular blockade from atracurium and vecuronium is virtually the same in patients with normal excretory function (Miller et al., 1984).

The short elimination half-life of atracurium was thought to be by Hofmann elimination and ester hydrolysis. However, Hofmann elimination may not be as dominant as was once believed. In fact, Fisher and colleagues (1985) found that nearly one-half of the clearance of atracurium from blood could not be accounted for by either Hofmann elimination or ester hydrolysis.

All the attempts to define precisely the mechanism by which atracurium is cleared from blood do not detract from its lack of dependence on the kidney or liver for its elimination. Only recently has the fate of some of its metabolites (of which at least nine have been identified by our laboratories) been examined. Because of its central nervous system stimulating properties, laudanosine has received the most attention. In their initial studies comparing the pharmacokinetics of atracurium in patients with and without renal failure, Fahey and colleagues (1984) found that laudanosine was readily formed and measured from a single i.v. dose of atracurium 0.5 mg kg\(^{-1}\). Although precise pharmacokinetic studies were not performed, the elimination half-life of laudanosine appeared to be several hours. Furthermore, the concentrations of laudanosine in patients with renal failure were higher than those in patients with normal renal function. This led to the speculation that laudanosine is dependent on the kidney for its elimination. However, subsequent studies in the dog revealed that laudanosine is primarily metabolized by the liver. Furthermore, these studies found that laudanosine easily crosses the blood–brain barrier (Hennis et al., 1984). Although these investigators found that extremely high doses of laudanosine were required to cause convulsions, Shi and colleagues (1985) found that laudanosine, in concentrations ranging from 400 to 800 ng ml\(^{-1}\), increases anaesthetic requirement (the minimum alveolar anaesthetic concentration, MAC) by 30%. Also, Lanier, Milde and Michen-
found no significant difference in duration of neuromuscular blockade from the initial dose or from repeated doses of atracurium. More recently, this same group (Hunter, Jones and Utting, 1984) compared vecuronium, atracurium and tubocurarine in patients with and without renal function. Both vecuronium and atracurium appeared to be little affected by the absence of renal function, whereas tubocurarine was longer-acting and less predictable. Thus, from the available studies, the pharmacokinetics of atracurium and vecuronium seem not to be affected by the absence of renal function. Our own preliminary studies indicate that vecuronium is more variable than atracurium in patients with no renal function.

HEPATIC DISEASE

Theoretically, the pharmacokinetics of atracurium should not be changed by an alteration in hepatic function. Ward and Neill (1983) were the first to examine the pharmacokinetics of atracurium in patients with hepatic failure. They studied six patients with fulminant hepatic failure. Five of these patients had hepatic failure induced by paracetamol, and the remaining patient had a failed liver transplant. The investigators found that the pharmacokinetics of atracurium 0.7 mg kg^{-1} i.v. were not significantly different from six additional patients undergoing routine, minor surgery, who had normal renal and hepatic function. The pharmacodynamics of atracurium were not studied by these investigators. Cook and colleagues (1984) studied 10 children, age 2-10 yr, six of whom had severe liver disease. They found that there were no important differences in the pharmacokinetics of atracurium 0.5 mg kg^{-1}. They also stated that there was no clinical difference in the recovery times of neuromuscular blockade between the two groups, although durations of neuromuscular blockade were not specified.

Bell and colleagues (1985) recently studied the characteristics of the neuromuscular blockades from both atracurium and vecuronium in patients with portal hypertension and some degree of liver dysfunction; they did not perform a pharmacokinetic analysis. Although the time from administration of atracurium to its peak response was prolonged in patients with liver disease, the duration of neuromuscular blockade was shorter. The same group also studied vecuronium 0.1 mg kg^{-1} as an initial dose with incremental doses of 0.04 mg kg^{-1}, and found nearly identical results as were found with atracurium. They

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RENAL FAILURE

As indicated previously, until the introduction of atracurium and vecuronium, all non-depolarizing neuromuscular blocking agents were heavily dependent on the kidney for their elimination (Miller and Savarese, 1981). Using very large doses of vecuronium (0.28 mg kg^{-1} and 0.14 mg kg^{-1}), Fahey and colleagues (1981) found that renal failure did not alter the duration of neuromuscular blockade or the pharmacokinetics of vecuronium in a small number of patients. Because of the relative insensitivity of the assay (high pressure liquid chromatography) used for their study, very large doses of vecuronium had to be administered. Now, with the availability of more sensitive and specific assays, such as gas chromatography, it is probable that more intense and comprehensive studies will be performed with vecuronium.

Fahey and colleagues (1984) performed the only study that has actually investigated the pharmacokinetics of atracurium in patients with and without renal failure. They studied 10 patients with normal renal function and 10 patients with renal failure sufficient to warrant cadaver kidney transplant. All patients were given atracurium 0.5 mg kg^{-1} i.v. They found that the onset time, duration of action, recovery time and pharmacokinetics of atracurium were not different between the two groups. Hunter, Jones and Utting (1982) administered atracurium to 25 patients with normal renal function and 21 patients who were anephric. They found no significant difference in duration of
concluded that atracurium may be a better drug in patients with severe liver dysfunction although, interestingly, their data do not support this conclusion. However, because 40–50% of an injected dose of vecuronium is eliminated in the bile, it would not be surprising to have the duration of a vecuronium neuromuscular blockade increased in patients who have significant liver dysfunction, and Lebrault and colleagues (1985) found that the elimination half-life and duration of neuromuscular blockade from pancuronium were prolonged in patients with cirrhosis. When all studies are combined, conclusions are similar. Liver disease is associated with a shorter duration of neuromuscular blockade from atracurium and vecuronium (< 0.15 mg kg\(^{-1}\)). When the dose of vecuronium is 0.2 mg kg\(^{-1}\) or larger, the duration will be prolonged (Hunter et al., 1985).

It can be concluded that atracurium and, to a lesser extent, vecuronium are the only two non-depolarizing neuromuscular blocking agents the pharmacokinetics of which appear not to be affected by renal failure. Conversely, atracurium is the only non-depolarizing neuromuscular blocking agent the pharmacokinetics of which are not altered by severe liver dysfunction. Vecuronium will be cleared at a slower rate when the dose exceeds 0.15 mg kg\(^{-1}\).

REFERENCES