The Pharmacokinetics and Pharmacodynamics of Atracurium in Patients with and without Renal Failure

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To determine the influence of renal function on the pharmacology of atracurium, 10 patients with normal renal function and 10 with renal failure (scheduled for cadaver kidney transplant) were anesthetized with nitrous oxide and halothane. Atracurium besylate, 0.5 mg·kg⁻¹, was given as an iv bolus and plasma samples were collected over a 4-h period. These samples were assayed for atracurium (all patients) and laudanosine, one of the principal metabolites (eight of the normal group), using an ion-exchange liquid chromatographic assay. The plasma concentrations of atracurium for each patient were fitted to a two-compartment pharmacokinetic model. The onset time, duration of action, and recovery time of atracurium neuromuscular blockade were measured. There were no differences found in the pharmacokinetics or pharmacodynamics of atracurium between patients with normal renal function and those with renal failure. There were measurable levels of laudanosine following atracurium administration with peak levels of 199 ± 31 ng·ml⁻¹ at 2 min. The authors conclude that the pharmacokinetics and pharmacodynamics of atracurium are not altered by renal failure. (Key words: Diseases; renal failure. Kidney: renal failure. Neuromuscular relaxants: atracurium. Pharmacodynamics: atracurium. Pharmacokinetics: atracurium besylate; laudanosine.)

STENLAKE ET AL.¹ recently synthesized a new medium-duration nondepolarizing neuromuscular blocking drug called atracurium (fig. 1). The major elimination pathway for this new drug is a nonenzymatic reaction, called Hofmann elimination, which rapidly breaks down atracurium to inactive metabolites. Studies in animals suggest that this chemical reaction renders elimination of atracurium from the body independent of renal function.² We therefore determined the influence of renal failure on the pharmacokinetics and pharmacodynamics of atracurium in anesthetized patients.

Methods

Twenty patients signed an informed consent statement that had been approved by the University of California Human Experimentation Committee. Ten of the patients were ASA Class I or II and scheduled for elective surgery. The remaining 10 patients were scheduled for a cadaver kidney transplant and had been dialyzed within 12 h prior to surgery. Approximately 90 min after the administration of diazepam, 10 mg po, anesthesia was induced with thiopental, 1–2 mg·kg⁻¹ iv, and inhalation of 60% nitrous oxide and halothane in oxygen via a face mask. Tracheal intubation was performed without the use of neuromuscular blocking drugs, and ventilation was controlled. Anesthesia was maintained with halothane at an end-tidal concentration of 0.6%, and nitrous oxide, 60%, as measured continuously by mass spectrometry. The PaCO₂ was maintained between 35 and 40 mmHg and pH between 7.35 and 7.40. Nasopharyngeal temperature was kept between 36.5 and 37.0°C by surface warming. Force of thumb adduction was quantified by a Grass® FT-10 force transducer in response to supramaximal stimuli (0.15 Hz, 0.15 ms duration) delivered to the ulnar nerve at the wrist (27-gauge steel needles) from a Grass® S44 stimulator.

Thirty to 45 min after induction of anesthesia, atracurium besylate, 0.5 mg·kg⁻¹, was given as a rapid iv bolus. Venous blood samples (5–10 ml) were drawn into heparinized syringes from a separate intravenous line at 2, 4, 6, 8, 10, 15, 20, 25, 30, 45, 60, 75, 90, 120, 150, 180, 210, and 240 min after the administration of atracurium. These blood samples were acidified immediately with 3 N sulfuric acid to a pH of 5.0 ± 0.5, centrifuged, and the plasma removed and stored at -20°C until analysis.

Plasma atracurium dibesylate levels were measured by an ion-exchange chromatographic assay, described by Neill and Jones,³ which we modified by introducing the use of d-tubocurarine as an internal standard. The assay was sensitive to 10 ng·ml⁻¹ of plasma and was linear over the range of the standard curve (10–10,000 ng·ml⁻¹ of plasma) with a coefficient of variation of 12% at 50 ng·ml⁻¹ and 3% at 8,000 ng·ml⁻¹.

During the study, further development of the assay

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allowed us to measure laudanosine, one of the major metabolites of atracurium, in eight patients with normal renal function. The assay for plasma levels of laudanosine differed from that for atracurium in that laudanosine methiodide, synthesized according to the procedure of Konda et al., was used as the internal standard and gradient rather than isocratic elution was employed (fig. 2). This assay was sensitive to 10 ng·ml⁻¹ and was linear over the range of the standard curve (10–8,000 ng·ml⁻¹) with a coefficient of variation of 9% at 15 ng·ml⁻¹ and 3% at 8,000 ng·ml⁻¹.

The plasma concentration versus time data for atracurium were fitted to two-compartment and three-compartment pharmacokinetic models using standard formulas; the choice of a two- or three-compartment model as the "best fit to the data" was made using statistical methods of Boxenbaum et al. We derived the following pharmacokinetic variables: distribution half-life (t₁/₂a), elimination half-life (t₁/₂β), clearance, volume of the central compartment (V₁), and volume of distribution (Vdₐrea). Mean values for these variables for each patient group were compared by unpaired Student's t test. The mean plasma level of laudanosine was determined for each sampling period for a group of eight normal patients.

The onset time (time from injection to maximal effect), the duration of action (time from injection to 95% return of control twitch tension), and the recovery time (time for twitch to go from 25 to 75% of the control twitch tension) of atracurium neuromuscular blockade were measured. The results were compared between the patient groups with the Mann-Whitney nonparametric statistical test.⁵
Table 1. Pharmacokinetic Data for Atracurium*

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>N</th>
<th>(t_{1/2a}) (min)</th>
<th>(t_{1/2b}) (min)</th>
<th>(V_1) (ml·kg(^{-1}))</th>
<th>(V_{\text{area}}) (ml·kg(^{-1}))</th>
<th>Clearance (ml·kg(^{-1})·min(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>10</td>
<td>5.4 ± 0.7</td>
<td>20.6 ± 1.2</td>
<td>60 ± 6</td>
<td>182 ± 12</td>
<td>6.1 ± 0.3</td>
</tr>
<tr>
<td>Renal failure</td>
<td>9</td>
<td>3.4 ± 0.4</td>
<td>23.7 ± 0.9</td>
<td>86 ± 12</td>
<td>224 ± 16</td>
<td>6.7 ± 0.6</td>
</tr>
</tbody>
</table>

* Values represent mean ± SEM.

Statistical differences were considered significant at the \(P < 0.05\) level.

Results

The plasma atracurium data were best described by a two-compartment model (fig. 3). There were no statistical differences found between the pharmacokinetic variables for the two patient groups (table 1). Mean plasma laudanosine levels (fig. 4) in patients with normal renal function peaked at 199 ± 31 ng·ml\(^{-1}\) (mean ± SEM) at 2 min after atracurium administration and slowly decreased over the next 4 h. Atracurium, 0.5 mg·kg\(^{-1}\), resulted in 100% peak depression of control twitch tension in all patients except for one patient with normal renal function who had 95% peak twitch depression. There was no difference in onset time, duration of action or recovery time between the two patient groups (table 2).

Discussion

Hofmann elimination is responsible in large part for the breakdown of atracurium. This chemical reaction involves disruption of C — N\(^+\) bonds in atracurium by anionic groups (such as OH\(^-\)) leading to the eventual formation of laudanosine and pentamethylenediacrylate (fig. 1).\(^1\) This reaction does not require enzymes and is enhanced in alkaline solutions and at temperatures in the physiologic range. Thus fluids and tissues throughout the body are ideal environments for Hofmann elimination of atracurium to occur.

Pharmacokinetic analysis of atracurium elimination in humans is difficult for two reasons. First, atracurium continues to break down by Hofmann elimination in venous blood samples. A pH of 5.0 ± 0.5 and storage of the serum at −20°C were found in this study to be the optimal conditions for inhibiting further breakdown of atracurium. Secondly, traditional two- and three-compartment models do not completely describe the pharmacokinetic variables for atracurium. These models are based on the assumption that elimination of a drug occurs from a single compartment, not the multicompartment elimination that happens with atracurium. Hull has suggested that, despite the deficiencies of the existing pharmacokinetic models, they do provide accurate estimates of clearance, \(t_{1/2a}\), \(t_{1/2b}\), and \(V_1\).\(^6\) The clinician, for example, can use the value for clearance to determine infusion rates of atracurium for use in long surgical procedures. However, the volume of distribution at steady state (\(V_{\text{area}}\)) cannot be accurately estimated by traditional models. Instead, \(V_{\text{area}}\), which is calculated using values for clearance and \(t_{1/2b}\), can be used. Accurate determination of \(V_{\text{area}}\) must await development of a pharmacokinetic model and sampling techniques that will account for the varying rates of elimination of atracurium from different compartments.

The pharmacokinetics of atracurium have been described previously by Ward et al. in healthy anesthetized

Table 2. Pharmacodynamic Data for Atracurium*

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>N</th>
<th>Onset (min)</th>
<th>Duration (min)</th>
<th>Recovery Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>10</td>
<td>1.8 ± 0.1</td>
<td>69.5 ± 5.2</td>
<td>10.55 ± 1.1</td>
</tr>
<tr>
<td>Renal failure</td>
<td>10</td>
<td>2.0 ± 0.4</td>
<td>77.4 ± 3.2</td>
<td>13.1 ± 3.2</td>
</tr>
</tbody>
</table>

* Values represent mean ± SEM.

\(^\dagger\) n = 7.

\(^\ddagger\) n = 8.
patients and in patients with severe hepatic and renal
disease being treated in the intensive care unit.7,8 Their
pharmacokinetic analysis, similar to that used in this
study, yielded results in normal patients that are similar
to those reported here. In the patients with combined
liver and kidney disease, Ward et al. found significant
increases in t1/2α, V1, and Vdarea above normal values,
with no change in clearance. The duration of neuro-
muscular blockade in these patients was not measured.
Our study suggests that the differences Ward et al.
observed between healthy anesthetized patients and
those in the intensive care unit may be due to hepatic
failure alone, since we demonstrated no effect of renal
failure on the pharmacokinetics or pharmacodynamics
of atracurium.

Atracurium thus represents the second new nonde-
polarizing neuromuscular blocker found to be useful in
renal failure patients. The first was vecuronium, which
was demonstrated, in a study similar to this one, to have
no alteration in pharmacokinetics or pharmacodynamics
when used in patients with renal failure.9 The unique
breakdown of atracurium by Hofmann elimination would
appear to explain the lack of effects that renal failure
has on its action, whereas rapid uptake and elimination by
the liver is the likely explanation for vecuronium.10
Thus, the clinician is now able to more safely provide
neuromuscular relaxation for patients with renal failure.

This study also has demonstrated that measurable
levels of laudanosine do occur after atracurium admin-
istration. The pharmacology of laudanosine is not well
established. Laudanosine is an alkaloid found in small
quantities in opium. In 1899, Babel showed that, in
several animal species, synthetic laudanosine caused con-
vulsive activity if given in high doses (e.g., 21 mg·kg⁻¹
in the rabbit).11 In 1955, Mercier and Mercier found
that 9–10 mg·kg⁻¹ of laudanosine was necessary to
produce an “epileptic pattern” in dogs monitored by
electroencephalogram; in one dog who had received 9
mg·kg⁻¹, the reinjection of 10 mg·kg⁻¹ of laudanosine
provoked a grand mal seizure.12 In 1983, Chapple and
Clark demonstrated that 4 mg·kg⁻¹ of laudanosine
produced no significant neuromuscular or cardiovascular
effects in cats.13 Although they did not comment on
neuromuscular effects, the cats were anesthetized with chlo-
ralose and pentobarbital, which may have suppressed
any seizure activity. The extent to which laudanosine
crosses the blood brain barrier and the blood concen-
tration necessary to produce convulsions in animals or
humans has not yet been determined. In addition, to
date, more than 150,000 surgical patients worldwide
have received atracurium and no seizure has been
reported.

In summary, we found that there was no difference
between the pharmacokinetics and pharmacodynamics
of atracurium in patients with normal renal function
and those with renal failure. Thus, atracurium appears
to be an ideal drug for patients with renal failure.

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