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Atracurium Decay and the Formation of Laudanosine in Humans

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Several groups of investigators have reported that the plasma concentrations of laudanosine, a metabolite of atracurium, are high immediately after administration of atracurium and thereafter decline. Such a time profile of a metabolite in plasma is very unusual. The authors describe a model of atracurium decay and laudanosine disposition that satisfactorily explains these data. The model reveals the following: 1) each atracurium molecule is degraded into two of laudanosine; 2) the generation of laudanosine occurs through two processes—a rapid one, involving approximately 31% of the atracurium dose and proceeding with a half-life of 0.25 min, and a slower one, involving the residual 69% and proceeding with a half-life of 51 min; 3) atracurium degradation by Hofmann elimination proceeds in the central and the noncentral compartments; 4) laudanosine formed from atracurium gains access to its central compartment and disappears from plasma in a biexponential pattern; 5) in cirrhotic patients, only 18% of the atracurium dose is degraded rapidly and laudanosine is disposed of more slowly. The authors propose that the rapid degradation of atracurium in plasma proceeds through a nucleophilic substitution reaction, with plasma nucleophiles substituting for the laudanosine moiety in atracurium. Because both laudanosine moieties in atracurium are required to establish and sustain plasma concentrations of laudanosine, excretion of atracurium or its degradation through pathways not generating laudanosine must be small. (Key words: Neuromuscular relaxants, atracurium: laudanosine. Pharmacokinetics.)

ATRACURIUM IS UNIQUE among drugs used clinically in anesthesia in that it was synthesized[1] to undergo a "spontaneous" (*i.e.*, nonenzymatic) degradation (Hofmann elimination). The products of this decay route of atracurium were predicted to be laudanosine and an acrylate moiety. Laudanosine was indeed detected in plasma of patients treated with atracurium. All investigators reported that the mean concentration of laudanosine, after an intubating dose of atracurium (0.5–0.6 $mg \cdot kg^{-1}$), was between 200 and 300 $ng \cdot ml^{-1}$ at 2 min after the intravenous (iv) injection of atracurium and that it declined transiently (up to the eighth or tenth minute). The concentration then leveled off before a final phase, during which the concentration decreased. This pattern was observed in normal patients[2–5] (including young and old patients[5]) and in patients with renal disease.[2] The pattern was different in patients with cirrhosis, however,[4] in that the concentration of laudanosine was initially (at 2 min after the iv administration of atracurium) only half of that observed in control patients. The laudanosine concentration continued to increase until approximately the 90th min, and only thereafter did it decrease progressively. No explanation of this very interesting and unusual time profile of laudanosine concentration in plasma has been offered. In general, plasma concentration of a metabolite is expected to start from zero at the time of administration of the parent drug, then increase, to reach a peak, and ultimately decrease.

Ward *et al.*[3] offered a model for laudanosine formation and distribution after the administration of atracurium. The authors proposed that laudanosine is produced from atracurium by a first-order reaction in its central compartment. The formation rate constant of laudanosine was assumed to be numerically equal to the rate constant for the elimination of atracurium from the central compartment. This model appears deficient for the following reasons: 1) there is no *a priori* reason to assume that the elimination of atracurium from the central compartment and the formation of laudanosine proceed at the same rate; 2) first-order formation of laudanosine from atracurium in the central compartment is incompatible with the observed early time profile of the laudanosine concentration in plasma; 3) the proffered model does not account for the possibility that up to two laudanosine molecules might be formed from one molecule of atracurium; 4) no values were reported for the rate constants for either the formation or the disposition of laudanosine; and 5) the question of what fraction of atracurium must be degraded to yield the amounts of laudanosine observed in plasma was not considered.[6,7]

The initially high plasma concentration of laudanosine is not likely to be an artifact arising from the contamination of the atracurium injection solution with laudanosine. The observed concentrations were too high to result from an inadvertent injection of laudanosine with atracurium because laudanosine was present in only trace amounts (Fahey[8]; and Hunter, personal communication). Additionally, the different time profile of laudanosine concentration in plasma of cirrhotic patients negates the contamination explanation.

Because the reported plasma concentrations of laudanosine thus appear to be real and not artifactual, we set out to examine the formation and disposition of lauda-

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nosine in patients exposed to atracurium. Our intentions were as follows: 1) to define the rate(s) of laudanosine generation; 2) to determine the amount of atracurium required to produce the reported plasma concentrations of laudanosine; and 3) to quantitate the disposition of laudanosine. If we were successful, the newly procured quantitative description of the data already reported by other investigators was expected to offer an explanation for the observed differences between the plasma concentrations of laudanosine in the control and cirrhotic patients.

We have based our approach on two assumptions: 1) in a semiquantitative way, the time profile of plasma concentrations of laudanosine resembles that of a drug injected as a bolus and as a continuous infusion; and 2) spontaneous decay of atracurium by Hofmann elimination occurs at rates similar *in vivo* and *in vitro*. Our proposed model of atracurium decay and laudanosine disposition in humans closely approximates the results reported by all investigators. Furthermore, it allows for a number of inferences to be drawn about the fate of atracurium and laudanosine in patients either with or without hepatic cirrhosis.

Materials and Methods

The data from Parker and Hunter[4] describing the concentrations of atracurium and laudanosine in plasma of normal and cirrhotic patients treated with atracurium were selected for analysis. Geometric means of the plasma concentrations were calculated for atracurium (13 observations from 2 to 90 min after the iv injection of atracurium, 0.6 $mg \cdot kg^{-1}$) and laudanosine (20 observations from 2 to 360 min) for seven normal and eight cirrhotic patients. All mass and concentration units were transformed to molar values to enable us to follow the conversion of the parent drug (atracurium) into its metabolite (laudanosine).

The following steps were considered in the formulation of the model:

1. Decay of atracurium by Hofmann elimination. Tsui *et al.*[9] reported that atracurium degrades in a monoexponential fashion *in vitro* under conditions similar to those *in vivo* (phosphate-buffered saline, *p*H 7.40 at 37° C). The decay could have been only apparently monoexponential, because the elimination reaction (Hofmann) is initiated by the abstraction of one proton by the hydroxyl group (to form a molecule of water). This initial step is dependent on the activity (concentration) of the hydroxyl group, and, hence, the reaction is enhanced by an increase in *p*H of the solution. The removal of a proton ultimately results in formation of two split products: laudanosine and an acrylate ester. The concentration of the hydroxyl group in a buffered solution and in the extracellular compartment of the body is constant. Therefore, the consumed hydroxyl group is instantaneously replaced, and the elimination reaction—although a bimolecular reaction—proceeds as an apparently monoexponential (first-order) process. In consideration of laudanosine formation, the decay of atracurium indicates that laudanosine cannot be formed at a rate faster than the rate of atracurium decay. Two extremes must be considered: 1) the most rapid formation of laudanosine will occur if both susceptible sites are cleaved at the same time, thus simultaneously forming two laudanosine molecules, and 2) if the cleavage at the two sites occurs in sequence, but with identical rates at both sites, then the same total amount of laudanosine will be generated at a slower rate. These considerations indicate that, although Hofmann elimination of atracurium proceeds as an apparent first-order reaction, the generation of laudanosine does not necessarily follow first-order kinetics.

   Because the prerequisites for Hofmann elimination of atracurium (*i.e.*, *p*H and temperature) in the *in vitro* study[9] were comparable to those *in vivo*, we postulated that the rates of the "spontaneous" degradation of atracurium and of the concomitant formation of laudanosine would also be comparable.
2. Disposition of atracurium *in vivo*. Atracurium disappears from plasma in a biexponential manner.[10,11] The rate of atracurium loss from plasma is much faster[10,11] than can be accounted for by the rate of Hofmann elimination measured at the same *p*H and temperature.[9] It is obvious that such a rapid disappearance of atracurium from plasma must result from either accumulation of atracurium in a "storage" compartment or excretion and metabolic degradation independent of Hofmann elimination. In constructing our model, the choice between these two possibilities was based on the consideration of the amount of atracurium necessary to generate laudanosine.
3. Laudanosine disposition *in vivo*. Currently there are no reports available about the disposition of laudanosine in humans after an iv administration of laudanosine. The only study of this nature was conducted on dogs.[12] The data were described in terms of a triexponential disappearance of laudanosine from plasma. For our model, and in the absence of any convincing reasons to the contrary, we assumed a simple biexponential disposition of laudanosine in humans, with elimination occurring only from the central compartment.
4. Formulation of a kinetic model for the simultaneous decay of atracurium and disposition of laudanosine in humans. Several constraints were placed on the model:

a. Conservation of mass. Disappearance of atracurium from plasma must be accounted for by its degradation, excretion, or temporary storage in a compartment. The amount of laudanosine formed from atracurium may range from 1) less than the injected amount of atracurium, if the excretion and degradation processes not producing laudanosine are involved, to 2) twice as much, if there is no excretion of atracurium and all degradation of atracurium is accompanied by the formation of laudanosine.
b. Degradation of atracurium accompanied by the production of laudanosine must proceed along chemically definable routes and at rates dependent on the environment (*p*H and temperature). Therefore, Hofmann elimination was postulated to proceed in the central and noncentral compartments of atracurium (*i.e.*, *p*H and temperature were assumed to be homogenous in the body spaces containing atracurium).
c. Laudanosine gains access to its central compartment independent of whether the decay of atracurium has occurred in atracurium's central or noncentral compartments. The constraint is plausible because laudanosine is a tertiary amine and, hence, has a larger central volume of distribution (V_c)[12] than does atracurium.[11] Expressed in other words, the body compartments of atracurium and laudanosine are not identical but may overlap.
d. The addition of laudanosine to its V_c is kinetically akin to the administration of laudanosine as an iv bolus and continuous supplementation. However, the sum of the amounts of laudanosine added by both modes must conform to constraint a (*i.e.*, the conservation of mass).

These considerations led us to the formulation of a kinetic model describing the concurrent decay of atracurium and disposition of laudanosine. A diagram of the postulated pathways of atracurium degradation and the generation of laudanosine is presented in figure 1. The principal characteristics of the model are as follows: 1) Rapid degradation of a fraction of the atracurium dose (denoted F in fig. 1) accounts for the fast addition of laudanosine to its central compartment. Both laudanosine groups are postulated to be cleaved rapidly. This process corresponds to the postulated iv bolus injection of laudanosine. The remaining amount of atracurium (denoted 1-F in fig. 1) is postulated to decay by Hofmann elimination, with the rate constant similar to that observed *in vitro*. Laudanosine formation by Hofmann elimination is postulated to occur sequentially, the first molecule of laudanosine being cleaved from atracurium and the second from the quaternary monoacrylate. (2) Laudanosine, generated by either of these two processes, is postulated to gain access to its central compartment. This compartment includes plasma (from which samples for the determination of laudanosine were collected). Laudanosine disappearance from plasma is postulated to follow a biexponential course.

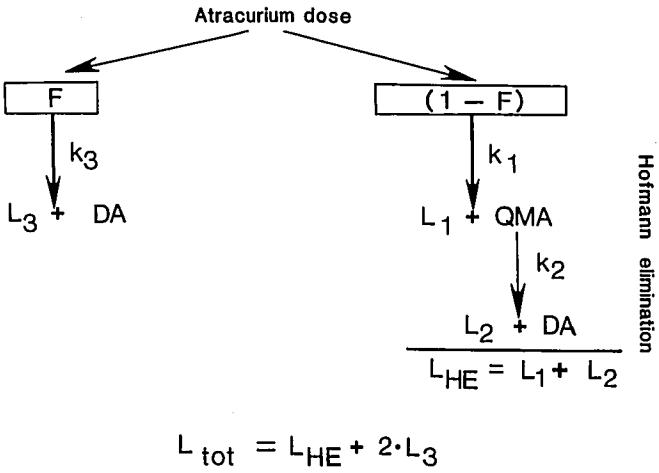

FIG. 1. The proposed model of the degradation of atracurium in humans. The fraction F of the dose of atracurium is rapidly degraded with the rate constant k_3 to form two molecules of laudanosine (L_3) and one molecule of diacrylate (DA). The fraction (1 − F) degrades *via* Hofmann elimination (rate constant k_1) to form a molecule of laudanosine (L_1) and quaternary monoacrylate (QMA). The latter degrades further (rate constant k_2) to form a second molecule of laudanosine (L_2) and diacrylate (DA). The sum L_{tot} ($2 \cdot L_3 + L_1 + L_2$) constitutes the amount of laudanosine formed in the body.

5. Analytic solution. The proposed model can be described in quantitative terms by a system of linear differential equations for the decay of atracurium and the disposition of laudanosine, both processes proceeding concurrently. The task of solving this system of differential equations was simplified by use of the Laplace transforms for the input and the distribution functions of laudanosine[13] (see Appendix). The Laplace transform for the amount of laudanosine in its central (plasma) compartment is then simply

$$\overline{{}_{p}Laud_a} = \overline{input}_{Laud} \cdot \overline{dist}_{Laud} \quad (1)$$

where

$\overline{{}_{p}Laud_a}$ = Laplace transform of the function describing the time profile of the amount of laudanosine in the plasma (sampled) compartment

$\overline{input}_{Laud}$ = Laplace transform for the input function of laudanosine into its (laudanosine's) central (plasma) compartment

$\overline{dist}_{Laud}$ = Laplace transform for the distribution function of laudanosine out of the central (plasma) compartment

To obtain an analogous expression for the plasma concentration of laudanosine, $\overline{{}_{P}Laud_c}$, $\overline{dist_{Laud}}$ was divided by laudanosine's V_c. Thus,

$$\overline{{}_{P}Laud_c} = \overline{input_{Laud}} \cdot \overline{dist_{Laud}}/V_c \quad (2)$$

The numeric inversion of $\overline{{}_{P}Laud_c}$ was accomplished with a commercially available program‡ for a microcomputer. The estimates for the parameters describing the input function of laudanosine (k_1 and k_2) were constrained by the previously outlined considerations regarding the decay of atracurium by Hofmann elimination. The initial estimates for the other parameters (F and k_3 for the input; and A, k_A, k_B, and V_c for the disposition of laudanosine) were modified to minimize the sum of squares of differences between the observed concentrations of laudanosine in plasma and the calculated values.

Biexponential curves were also fitted to the data on the plasma concentrations of atracurium in normal and cirrhotic patients with the use of the Laplace transformation. Laplace transform for the input after a bolus injection of a drug is the dose of the drug,[13] and the Laplace transform for the distribution was formulated as appropriate for a biexponential disposition (see Appendix). The fit of the curves to the observed data was optimized by adjusting the estimates for the biexponential disposition and for V_c of atracurium to minimize the sum of squared differences between the observed data and the calculated curve.

Results

Results from the computer simulation of the formation of laudanosine by Hofmann elimination of atracurium in a closed system *in vitro* are illustrated in figure 2. In these calculations, it was assumed that the degradation of atracurium proceeds at an identical rate in all three instances. Laudanosine was formed less rapidly if the elimination reaction occurred first on atracurium and subsequently on the intermediary product, quaternary monoacrylate (fig. 2, upper panel), than if both laudanosine molecules were liberated simultaneously from atracurium (fig. 2, middle panel). However, even with the assumption that laudanosine would be formed in the body by Hofmann elimination at the fastest rate possible, the plasma concentration of laudanosine was projected to peak during the second hour after the administration of atracurium to humans (fig. 2, lower panel). Thus, generation of laudanosine solely by Hofmann elimination is not adequate to account for the rapid initial appearance of laudanosine in plasma.

‡ Laplace® from MicroMath, Salt Lake City, Utah.

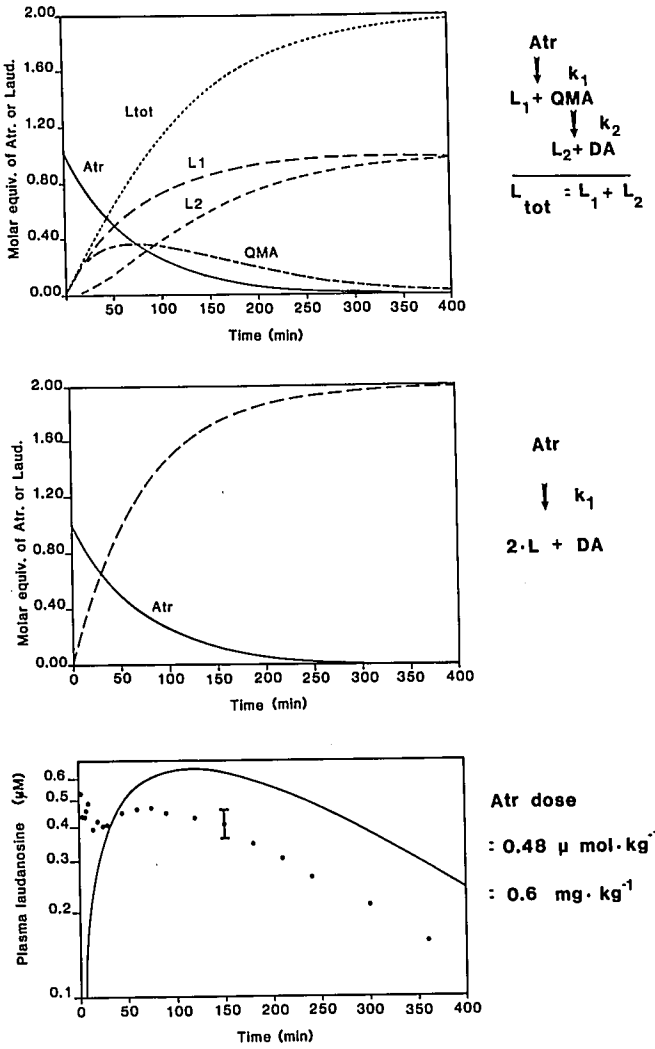

FIG. 2. Computer simulation of the quantitative aspects of atracurium's decay *via* Hofmann elimination and the concurrent formation of laudanosine. (*Top*) Degradation of atracurium and formation of laudanosine in a closed system *in vitro* at *p*H 7.4 and 37° C. The rate constant k_1 has a value similar to that found by Tsui *et al.*[9] for buffered saline (*p*H 7.4, 37° C). Laudanosine is formed in sequence, the first molecule (L_1) from atracurium (Atr), and the second (L_2) from the quaternary monoacrylate (QMA). DA = diacrylate. Eventually two laudanosine molecules are formed from one molecule of atracurium. (*Center*). Simultaneous formation of two molecules of laudanosine (L, dashed line) by the decay of atracurium (Atr) *via* Hofmann elimination. *In vitro* conditions were assumed to be identical to those in the top graph. Although the decay of atracurium proceeds at the same rate as in the top graph, the amount of laudanosine formed early is larger. (*Bottom*) Expected plasma concentration of laudanosine (curve) if the fastest rate of laudanosine formation as shown in the center graph is assumed to proceed in the body. The disposition parameters for laudanosine are similar to those derived from our model for healthy patients. The poor fit of the curve to the data of Parker and Hunter[4] (points) is evident.

When the injected amount of atracurium is formally partitioned into one fraction (F in fig. 1) that decays very rapidly and a fraction (1-F) that decays sequentially by

Hofmann elimination, an input function of laudanosine is generated that allows for a rapid and continued appearance of the metabolite. Optimization of the parameters for the formation (F and k_3) and disposition of laudanosine (A, k_A, k_B, and V_c) provides a very satisfactory time profile of laudanosine in plasma. A close agreement is evident between the measured concentrations reported for the control (fig. 3) and cirrhotic (fig. 4) patients on the one hand, and the calculated values obtained from the model for either group of patients, on the other. The difference in the formation and disposition of laudanosine between the control and cirrhotic patients results from differences in 1) the size of the fraction of atracurium dose that decays rapidly (table 1), and 2) the rate of disappearance of laudanosine from plasma (table 2). The V_c of laudanosine does not appear to differ between the two groups (table 2).

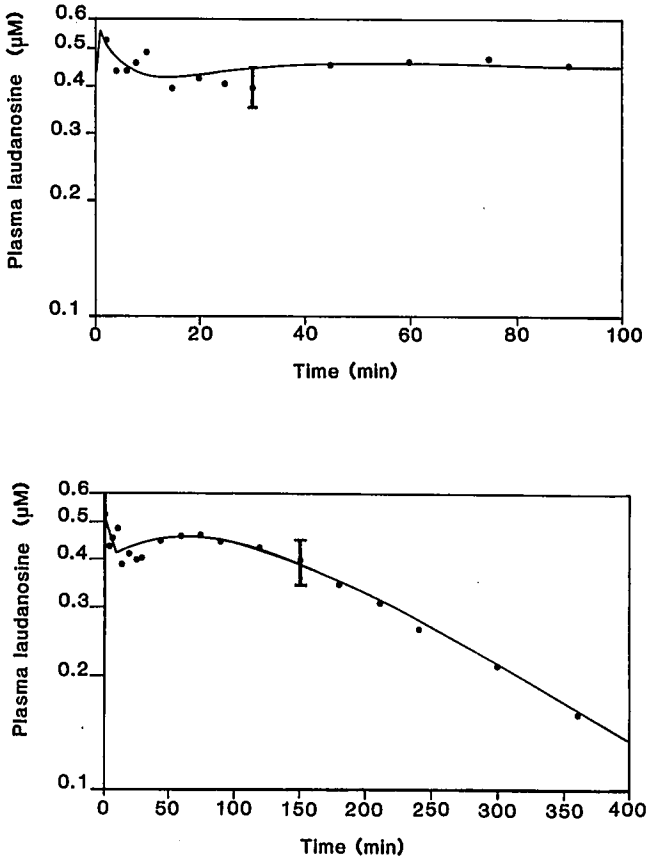

FIG. 3. Plasma concentrations of laudanosine in healthy patients to whom atracurium was administered intravenously (0.6 $mg \cdot kg^{-1}$ = 0.48 $\mu mol \cdot kg^{-1}$). Closed circles represent the observations reported by Parker and Hunter.[4] Pooled standard error, appropriate for each mean value, is indicated only once. The line was obtained from the present model with the parameters for atracurium decay presented in table 1 and those for the disposition of laudanosine in table 2. At the time of the injection of atracurium, laudanosine was not present in plasma and initially its plasma concentration increased (*top*).

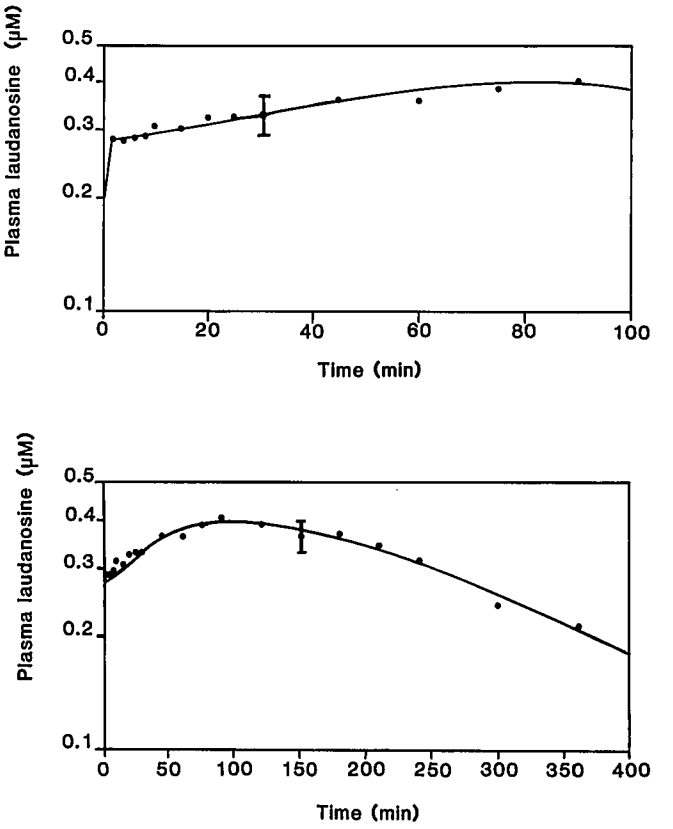

FIG. 4. Plasma concentrations of laudanosine in patients with hepatic cirrhosis to whom atracurium was administered intravenously. For details see the legend to figure 3.

Discussion

If it is assumed that the purpose of a pharmacokinetic model is a quantitative simulation of the observed plasma concentration of a drug, the proposed model fulfills this goal by satisfactorily describing the plasma concentrations of laudanosine after an iv bolus injection of atracurium. Before the inferences from the newly developed model are presented, the underlying assumptions must be examined critically.

1. Because of the electron-attracting property of the reverse ester group in atracurium, the bonds are weak between the alpha-carbonyl carbon and either of the two hydrogens bonded to it. In the presence of a base, one hydrogen is readily transferred (as a proton) from atracurium to the receiving base. The electronically disturbed atracurium molecule undergoes rearrangement by cleaving off the quaternary nitrogen as a tertiary amine (laudanosine) and accommodating the leftover electron pair as a second bond between the alpha- and beta-carbonyl carbons of an olefin residue. Because of its very high basicity and relative abundance, the hydroxyl group plays the role of the rate-

TABLE 1. Estimates of the Parameters for the Degradation of Atracurium in Healthy and Cirrhotic Patients

Parameter	Unit	Description	Healthy Patients	Cirrhotic Patients
F		Fraction of the dose that decays rapidly	0.313	0.175
k_3	min^{-1}	Rate constant for the rapid decay	2.8	2.8
$t_{1/2}$	min	Half-life corresponding to k_3	0.25	0.25
(1 − F)		Fraction of the dose that decays *via* Hofmann elimination	0.687	0.825
$k_1 = k_2$	min^{-1}	Rate constant for Hofmann elimination	0.0135	0.019
$t_{1/2}$	min	Half-life corresponding to $k_1 = k_2$	51.3	58.4

The parameters correspond to those presented in figure 1. The listed values provide the optimal estimates for the input of laudanosine.

governing base. This consideration lends support for our assumption that Hofmann elimination proceeds at a similar rate *in vivo* as well as *in vitro* in a solution buffered to *p*H 7.4 at 37° C. Logically, if the decay of atracurium proceeds more quickly *in vivo* than could be expected from the *in vitro* observations, then an alternative degradation pathway of atracurium *in vivo* would have to be assumed, either with or without concomitant formation of laudanosine.

2. Because even the maximal rate for the formation of laudanosine by Hofmann elimination could not account for the high plasma concentrations observed during the first 30 min after the administration of atracurium (fig. 2, lower panel), an additional, faster degradation pathway was postulated. However, this faster decay process cannot pertain to the whole dose of atracurium because otherwise there would be no atracurium left in the body to exert the pharmacologic effect. Formally, we expressed this constraint by limiting the amount of atracurium that is decaying by this postulated rapid mechanism and denoted this fraction of atracurium dose as F in figure 1. The magnitude of F and the corresponding rate constant (k_3 in fig. 1) establish the initial plasma concentration of laudanosine. The very high value of the rate constant for this degradation pathway (k_3 in table 1) implies that the two laudanosine molecules may be set free either simultaneously or in sequence. The data presently available are not sufficient to allow a decision to be made. The degradation of atracurium by this pathway was essentially completed by 2 min after the administration of atracurium. Therefore, the fraction F of the atracurium dose has already disappeared from plasma even before the first blood sample has been collected. However, the high plasma concentration of laudanosine at 2 min after the administration of atra-

TABLE 2. Estimates of the Parameters for the Biexponential Disposition of Atracurium and Laudanosine from Plasma of Patients Treated with Atracurium

	Atracurium $[Atr]_P = \frac{\text{Dose of Atr}}{V_C}(A \cdot e^{-k_A \cdot t} + B \cdot e^{-k_B \cdot t})$			Laudanosine $[Laud]_P = \frac{2 \cdot \text{Dose of Atr}}{V_C}(A \cdot e^{-k_A \cdot t} + B \cdot e^{-k_B \cdot t})$	
Parameter	Unit	Healthy Patients	Cirrhotic Patients	Healthy Patients	Cirrhotic Patients
A	fraction	0.74	0.74	0.43	0.51
B = (1 − A)	fraction	0.26	0.26	0.57	0.49
k_A	min^{-1}	0.2243	0.1906	0.215	0.0378
$_At_{1/2}$	min	3.09	3.64	3.22	18.3
k_B	min^{-1}	0.0349	0.0301	0.0082	0.0061
$_Bt_{1/2}$	min	19.9	23.1	84.5	113.7
V_C	$ml \cdot kg^{-1}$	69.4	100.8	490	605
Coefficient of determination*		0.998	0.998	0.937	0.956

The values provide the best fit to the data reported by Parker and Hunter.[4] The dose of atracurium (Atr) is in $\mu mol \cdot kg^{-1}$ and the plasma concentrations of laudanosine ($[Laud]_P$) or atracurium ($[Atr]_P$) are in $\mu mol \cdot L^{-1}$.

V_C = central volume of distribution.

* An estimate of the goodness of fit of the calculated curve to the data. It is the fraction of the total variance accounted for by the model and represents a more rigorous criterion of the fit than the correlation coefficient.

curium provides evidence that, in the control patients, approximately one third of the atracurium dose (F = 0.313) was degraded in plasma within a few circulation times.

3. The proposed pharmacokinetic model of the concurrent formation (from atracurium) and disposition of laudanosine yields a set of differential equations. The formulation and numeric solution would be very involved were it not for a method of converting the differential equations (expressed in time domain) to their Laplace transforms (expressed in the domain of the time-independent Laplace operator, s). Laplace transforms are formulated in algebraic terms and, hence, are easier to manipulate. The inversion of the Laplace transforms back into the time domain was accomplished, and indeed made possible, by the use of a microcomputer program. The advantage of this approach is evident from the simple form of the equation describing the time-dependent plasma concentration of a drug in terms of an input and a distribution function—equation 2.[13,14] Even with the use of this approach, many recalculations of the model were required to define the optimal parameters of the curves that best fit the observed data.

The current model of simultaneous decay of atracurium and disposition of laudanosine in normal patients provides, in plausible terms, a description of the events after the iv bolus injection of atracurium in humans (numeric estimates for the parameters are presented in tables 1 and 2). Approximately 31% of the atracurium dose is very rapidly (half-life, 0.25 min) degraded to yield two laudanosine molecules from each molecule of atracurium. The residual 69% of the dose decays with a half-life of approximately 50 min. The rate is close to that reported by Tsui *et al.*[9] for the degradation of atracurium by Hofmann elimination. It is important to stress that the model requires that the whole dose of atracurium be available for degradation by processes that result in production of laudanosine (two from each molecule of atracurium). Minor losses of atracurium by processes not resulting in the formation of laudanosine (*e.g.*, urinary[3] or biliary excretion) and the hydrolysis of the ester bonds cannot be excluded, but the amount of atracurium not available for the production of laudanosine must be small.

The tentative conclusion that all, or nearly all, of the atracurium dose decays to produce laudanosine is based on the acceptance of the estimate of V_c for laudanosine as presented in table 2. Because the V_c represents a proportionality constant relating the drug concentration in plasma to the amount of the drug in the body at time zero,[13] the proposed model reveals only the ratio of the V_c of laudanosine to the fraction of atracurium dose that decays to laudanosine. However, a significantly smaller value for V_c of laudanosine than the one reported in table 2 for normal patients is not likely in view of the chemical characteristics of laudanosine (see below) and the findings in dogs.[12] Therefore, we propose that all, or nearly all, of the atracurium dose decays to produce laudanosine.

Formation of laudanosine in cirrhotic patients proceeds at approximately the same rates as in the control patients (k_1, k_2, and k_3 in table 1). Only the amount of atracurium that decays rapidly (F in table 1) is different—approximately half of the amount in control patients. The parameters describing the disposition of laudanosine reveal that the disappearance of laudanosine from plasma is slowed in cirrhotic patients (table 2). Involvement of the liver in removing laudanosine from plasma is implicated. This conclusion is in agreement with the previous findings in humans.[15] The V_c of laudanosine is apparently somewhat larger in these patients (table 2). In view of the high lipid solubility of laudanosine and its low affinity for plasma proteins,[16] it is not surprising that hepatic cirrhosis has only a small influence on the V_c of laudanosine.

The model cannot disclose the nature of the process that rapidly degrades one third of the atracurium dose. However, the following interpretation is possible. If it is assumed that atracurium reacts rapidly with a component in plasma to produce laudanosine (*i.e.*, a bimolecular reaction), then the rate of laudanosine formation will be proportional to the product of the concentrations of atracurium and the unknown compound, X. The rapid dilution of atracurium in plasma and the availability of X that is probably restricted, as well as the depletion of X in the reaction with atracurium, combine to limit the amount of atracurium degraded through this pathway to approximately 30% of the dose. Provision of X from tissue stores probably restores X in plasma, but, by this time, the dilution of atracurium in plasma makes this reaction less efficient in terms of laudanosine production. In cirrhotic patients, the availability of X in plasma must be even more limited, and only half as much of the atracurium dose is rapidly degraded. We propose that X represents various nucleophiles—*i.e.*, compounds containing electron-rich groups like the mercapto or amino groups—and that the rapid degradation process is likely to be a nucleophilic substitution reaction.[17] Diminished concentration of thiol nucleophiles in plasma of cirrhotic patients[18,19] provides support for this interpretation.

The parameters describing the biexponential disappearance of atracurium from plasma are presented in table 2. The estimates for the distribution and elimination half-lives and for the V_c are based on the dose of atracurium of 0.6 $mg \cdot kg^{-1}$ (= 0.48 $\mu mol \cdot kg^{-1}$) and were obtained with the Laplace transformation. The results concur with those obtained by the conventional pharmacokinetic analysis.[4] The form of the biexponential function for the disappearance of atracurium from plasma in table 2 was

deliberately selected to make it applicable for any dose of atracurium (assuming linearity of the pharmacokinetic model) and to point out that approximately three fourths of the atracurium dose (A in table 2) disappears from plasma rapidly, whereas the residual one fourth of the dose (B in table 2) disappears with the half-life of approximately 20 min. There were no major differences between the healthy patients and those with hepatic cirrhosis in terms of the coefficients and exponents of the biexponential decay, although the V_c of atracurium, analogous to the findings of Parker and Hunter,[4] appears to be increased in the latter.

Because all of the atracurium dose is required to establish and sustain the observed plasma concentrations of laudanosine, the distribution of atracurium between the central and noncentral compartments[11] represents only a translocation of atracurium and cannot be interpreted as an irreversible loss of atracurium by excretion or metabolism not resulting in the formation of laudanosine. The previously reported "organ clearance" of atracurium[20,21] can now be interpreted as a process of the temporary storage of atracurium in the noncentral compartment. The "stored" amount of atracurium is still available, however, for the production of laudanosine.

The current model suggests—among other possibilities—that, in healthy patients, only two thirds of the actually administered dose of atracurium can be pharmacologically active. One third of the administered dose disappears rapidly and leaves behind—as the only trace—high initial plasma concentrations of laudanosine.

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Appendix

Program Steps for the Calculation of the Estimate for the Parameters of the Curve Describing the Plasma Concentrations of Laudanosine

$$L1 := K1 \cdot ATRD \cdot (1 - F)/(S + K1)$$
$$L2 := K1 \cdot K2 \cdot ATRD \cdot (1 - F)/((S + K1) \cdot (S + K2))$$
$$L3 := 2 \cdot K3 \cdot ATRD \cdot F/(S + K3)$$
$$INPUT := L1 + L2 + L3$$
$$DIST := (A/(S + KA) + (1 - A)/(S + KB))/V_C$$
$$PL := INPUT \cdot DIST$$

Where:

$ATRD$ = dose of atracurium ($\mu mol \cdot kg^{-1}$)

V_C = the central volume of distribution of laudanosine (L) ($l \cdot kg^{-1}$)

PL = Laplace transform of the plasma concentration of laudanosine ($\mu mol \cdot L^{-1}$)

S = Laplace operator

L1, L2, L3, K1, K2, K3, and F correspond to the symbols in figure 1 and table 1. A, (1 − A), KA, and KB correspond to the coefficients and exponents for laudanosine disposition (table 2).

Program Steps for the Calculation of the Estimates for the Coefficients and Exponents of the Curve Describing the Plasma Concentration of Atracurium

INPUT : = ATRD

DIST : = (A/(S + KA) + (1 − A)/(S + KB))/V_C

PATR: = INPUT · DIST

Where:

ATRD = the dose of atracurium ($\mu mol \cdot kg^{-1}$)

PATR = Laplace transform of the plasma concentration of atracurium ($\mu mol \cdot 1^{-1}$)

V_C = the central volume of distribution of atracurium ($l \cdot kg^{-1}$)

S = Laplace operator

A and (1 − A) are the coefficients and KA and KB the exponents of the biexponential function describing the disposition of atracurium from plasma (table 2).