Anesthesiology
72:145–152, 1990

# *Plasma Concentrations of Laudanosine, but Not of Atracurium, Are Increased during the Anhepatic Phase of Orthotopic Liver Transplantation in Pigs*

*Jean-François Pittet, M.D.,* Edömer Tassonyi, M.D.,† Corinne Schopfer, Pharm.D.,‡ Denis R. Morel, M.D.,§ Gilles Mentha, M.D.,¶ Marc Fathi,** Claude Le Coultre, M.D.,†† Daniel A. Steinig, M.D.,¶ Achille Benakis, Ph.D.‡‡*

**To quantify the changes in plasma concentrations of atracurium and laudanosine induced by the lack of hepatic function and circulation, the authors studied nine domestic pigs (22–25 kg) undergoing an orthotopic liver transplantation, and three control animals without surgery, using atracurium as the muscle relaxant. After intubation facilitated by isoflurane 2–3%, anesthesia was maintained with isoflurane (0.5% in oxygen) and fentanyl (4 $\mu g \cdot kg^{-1} \cdot hr^{-1}$). Ventilation was controlled to keep end-tidal $CO_2$ at 35–40 mmHg, body temperature maintained at 35.5–37.5° C, and arterial *p*H at 7.35–7.50. The right sciatic nerve was stimulated with a nerve stimulator delivering a single twitch at 0.1 Hz with 0.2-ms duration, at supramaximal stimulation. The force of the corresponding evoked isometric muscle contraction was continuously measured by a force-displacement transducer. A single iv bolus of atracurium (2 mg/kg) was given to obtain a 90–95% twitch depression, followed 5 min later by a constant-rate iv infusion of atracurium at 120 $\mu g \cdot kg^{-1} \cdot min^{-1}$ maintained during the entire investigation. Blood samples for plasma atracurium and laudanosine concentrations were drawn every 15 min. In the control group, plasma concentrations of atracurium remained stable between 6.5–8.0 $\mu$g/ml following initial bolus injection; plasma concentrations of laudanosine increased during the first 60 min, then remained stable between 0.69–0.74 $\mu$g/ml up to the end of the study. In animals undergoing transplantation, plasma concentrations of atracurium remained stable between 10–12 $\mu$g/ml, despite a 90-min duration of liver exclusion. In contrast, plasma concentrations of laudanosine were significantly increased 45 min after the hepatic vessels were clamped (from 0.57 ± 0.03 $\mu$g/ml to 0.91 ± 0.02 $\mu$g/ml, mean ± SE, $P < 0.05$), increased further to peak values of 1.24 ± 0.05 $\mu$g/ml after 90 min, and remained at these elevated concentrations after restoration of circulation to the transplanted liver. The results of the present study demonstrate that in pigs plasma clearance of atracurium does not depend on hepatic function. In contrast, plasma clearance of its major metabolite laudanosine is strongly dependent on liver function. (Key words: Liver: transplantation. Measurement techniques: high performance liquid chromatography. Neuromuscular relaxants: atracurium. Pharmacokinetics: atracurium; laudanosine. Sympathetic nervous system, catecholamines: norepinephrine.)**

THE EFFECTS OF IMPAIRED LIVER function on the metabolism of atracurium are not entirely clear since contradictory results have been reported in the literature.[1,2] For instance, elimination half-life of atracurium has been found unchanged in adult patients with liver failure after paracetamol intoxication.[1] Similarly, no difference has been found in the pharmacokinetic parameters of atracurium between healthy children and children with acute liver failure.§§ However, atracurium-induced neuromuscular (NM) blockade was significantly prolonged in primates after ligation of liver vessels[2] or in patients during the anhepatic phase of liver transplantation.[3] Thus, it is still unclear whether the pharmacokinetics and pharmacodynamics of atracurium are significantly modified in absence of liver function.

Laudanosine, a major metabolite of atracurium, is metabolized by the liver and excreted in the bile and urine.[4] At high plasma concentrations (greater than 7.9 $\mu$g/ml), it has been shown in cats to induce arterial hypotension, atrial and ventricular arrythmias, and seizure-like activity.[5] Furthermore, laudanosine was reported to induce the release of norepinephrine in vitro.¶¶ Plasma concentrations of laudanosine achieved in patients with impaired renal function are well below those associated with above described side effects.[6] Whether plasma concentrations of laudanosine reach toxic values with failing liver function is unknown.

The purpose of the present study was to quantify changes in plasma concentrations of atracurium and laudanosine induced by the lack of hepatic function and circulation and to evaluate the relationship between plasma concentrations of laudanosine and norepinephrine during orthotopic liver transplantation in pigs.

* Research Fellow in Anesthesia, Department of Anesthesiology.
† Staff Anesthetist, Department of Anesthesiology.
‡ Research Fellow, Department of Pharmacology.
§ Research Associate in Anesthesia, Department of Anesthesiology.
¶ Research Fellow in Surgery, Department of Surgery.
** Staff Chemist, University Hospital of Geneva.
†† Staff Surgeon, Department of Surgery.
‡‡ Staff Pharmacologist, Department of Pharmacology.

Received from the Laboratory of Experimental Surgery, Department of Surgery and Anesthesiology, and Department of Pharmacology, University Medical Center, Geneva, Switzerland. Accepted for publication August 28, 1989. Presented in part at the American Society of Anesthesiologists Annual Meeting, October 1988, San Francisco, California.

Address correspondence to Dr. Pittet: Département d'Anesthésiologie, Hôpital Cantonal Universitaire, 1211 Genève 4, Switzerland.

§§ Cook DR, Brandom BW, Stiller RL, Woelfel MD, Lai A, Slater J: Pharmacokinetics of atracurium in normal and liver failure patients (abstract). ANESTHESIOLOGY 61:A433, 1984.

¶¶ Nagashima H, Vizi ES, Kobayashi O, Kinjo M, Duncalf D, Goldiner PL, Foldes FF: Atracurium and laudanosine increase 3H-Norepinephrine release from guinea pig atrium (abstract). ANESTHESIOLOGY 65:A413, 1986.

## Methods

Twelve pigs (*suis scrofa domesticus*) weighing 22–25 kg were included in the study, after approval of the ethical committee on animal research of our institution. Animals were divided into two groups: a control group (n = 3) and an experimental group (n = 9). Animals from the control group received an identical anesthetic technique, but without surgery.

### Procedure

Each animal received azaperon 4 mg/kg, ketamine 7.5 mg/kg, and fentanyl 2 μg/kg im and 30 min later was anesthetized with isoflurane 2–3% in oxygen. The trachea was intubated without the use of a muscle relaxant and anesthesia was maintained with isoflurane (0.5% in oxygen) and fentanyl (4 $\mu g \cdot kg^{-1} \cdot h^{-1}$). Ventilation was controlled to keep arterial $P_{CO_2}$ at 35–40 mmHg, and body temperature was maintained at 35.5–37.5° C with thermoblankets. Normal saline was infused intravenously through a jugular vein at 10 $ml \cdot kg^{-1} \cdot h^{-1}$. Mean systemic arterial pressure and central venous pressure were measured using a carotid arterial cannula and a central venous catheter, respectively, connected to calibrated quartz pressure transducers (1290 A Hewlett-Packard®), positioned at the midaxillary line, and recorded on a chart recorder (78172 A Hewlett-Packard®). During the entire investigation, arterial *p*H was maintained within the range of 7.35–7.50 with sodium bicarbonate, if necessary. The right posterior leg of the pig was immobilized and the sciatic nerve was surgically isolated, and directly stimulated with a nerve stimulator (Laubscher P1 NS-2B) delivering supramaximal stimuli of 0.2-ms duration at 0.1 Hz frequency. The corresponding evoked isometric muscle contraction was continuously recorded by a Grass FT-10 force-displacement transducer on a one-channel recorder (Kipp and Zonen® BD 8). After a stable anesthetic level was established for at least 30 min, a single iv bolus injection of atracurium of 2 mg/kg was administered, followed 5 min later by a constant rate iv infusion of atracurium at 120 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during the entire investigation. Blood samples for atracurium and laudanosine concentrations were drawn every 15 min, for norepinephrine concentrations every 60 min, from 30 min, after the beginning of atracurium infusion up to the end of operation.

In a preliminary study, we found that a 2 mg iv bolus of atracurium followed 5 min later by a constant-rate iv infusion of atracurium at 120 $\mu g \cdot kg^{-1} \cdot min^{-1}$ resulted in a stable 90–95% twitch depression during the entire study period. We also determined in five pigs the pharmacokinetics of a 2-mg iv bolus of atracurium, taking arterial blood samples at 0, 2, 5, 7, 10, 15, 30, 45, 60, 75, and 90 min after atracurium injection. Data for plasma concentrations of atracurium were fitted to a two-component exponential by weighted nonlinear least squares analysis and kinetic parameters calculated using the convention of Ward *et al.*[7]

The surgical procedure consisted of three parts: 1) a phase of preparation of the vessels for the placement of the cavo-porto-jugular bypass and the dissection of hepatic ligaments and vessels to allow the hepatectomy; 2) an anhepatic phase with drainage of the splanchnic circulation using an external veno-venous bypass; and 3) a last phase after recirculation of the graft with an end-to-end anastomosis of the hepatic artery and cholescysto-duodenostomy. The duration of the surgical procedure in the experimental group was 240–360 min.

### Determination of Plasma Concentrations of Atracurium and Laudanosine

A previously described[8] high performance liquid chromatography (HPLC) assay for atracurium and laudanosine plasma concentration determination requires the use of a gradient solvent elution. We have developed a simplified method using solid phase extraction of plasma followed by isocratic ion-exchange HPLC with a strong cation exchange column kept at room temperature.

Atracurium and laudanosine were supplied by the Welcome Foundation (Dartford, UK). D-tubocurarine, acetonitrile, methanol (HPLC grade) and all other chemicals were supplied by Fluka (Buchs, FRG) and were of analytical grade. Water was glass bidistilled.

One milliliter of whole blood was collected in a heparinized tube and immediately centrifuged at 5,000*g* for 30 s; 200 μg of plasma were transferred in an Eppendorf tube containing 800 μg of 0.015 M sulfuric acid. The tube was quickly frozen to −70° C in acetone and dry ice. Samples were stored at −70° C until analyzed. Samples were spiked with 20 μg of a d-tubocurarine solution (100 μg/ml) and extracted with Bond Elut Phenyl cartridges according to the method of Simmonds[8] without evaporating the eluate. Fifty micrograms of this solution were used for HPLC determination. HPLC was carried out using a Spherissorb S 5 CN 250 × 4 mm (Knauer, Belmont, Switzerland) column linked to a fluorescence detector spectrofluorometer SFM 23 (Kontron, Bern, Switzerland) set at 280 nm (excitation) and 230 nm (emission) and with a Rheodyne 7020 injector. The chromatographic system was used at room temperature. Mobile phase consisted of acetonitrile 6 g/l sodium sulfate (60/40) in 0.02 M sulfuric acid. It was used at a flow rate of 1.5 ml/min. Under these conditions, the retention times of laudanosine, d-tubocurarine, and atracurium were 2.5, 3.6, and 6.8 min, respectively. Plasma and other anesthetic agents did not interfere in the determination of these assays.

TABLE 1. Pharmacokinetic Variables of Atracurium in Pigs and Humans after iv Bolus Injection

| | Pig | Human* | P |
|---|---|---|---|
| $T_\alpha$ (min) | 2.1 ± 0.1 | 2.3 ± 0.3 | NS |
| $T_\beta$ (min) | 28.6 ± 6.3 | 19.3 ± 0.9 | NS |
| $Cl_{tot}$ (ml · min$^{-1}$ · kg$^{-1}$) | 9.7 ± 2.0 | 5.5 ± 0.3 | NS |
| Vdl (ml/kg) | 383 ± 57 | 153 ± 13 | <0.05 |

Mean data ± SE of five animals and six humans. $T_\alpha$: Distribution half-life. $T_\beta$: Elimination half-life. $Cl_{tot}$: Total clearance of the drug from the body. Vdl: Apparent volume of distribution.
* Human data from reference Ward and Weatherley.[28]

A calibration curve was generated by plotting peak area against known drug concentrations. Standard samples were prepared with pig plasma added to atracurium at concentrations ranging from 3 to 24 μg/ml and laudanosine at concentrations from 0.6 to 3 μg/ml. Correlation coefficients were 0.9997 for atracurium and 0.9982 for laudanosine. Detection limits were 0.05 μg/ml for atracurium and 0.01 μg/ml for laudanosine. Recovery of analytes from plasma was at least 95% in all cases.

### Determination of Plasma Concentrations of Norepinephrine

Two milliliters of pig whole blood were collected in a heparinized tube and immediately centrifuged at 5,000*g* for 30 s; 1 ml of plasma was transferred in an Eppendorf tube and quickly frozen to −70° C in acetone and dry ice. Samples were stored at −70° C until analyzed. Plasma was separated on activated aluminium oxide. Norepinephrine was eluted by 0.1 M perchloric acid using a Beckman pump (Mod 110 B) and a pulse dampener (Portmann Instrument, Switzerland), analyzed by reverse-phase HPLC using a Beckman column (Mod C 18, 5 μm, Ultrasphere® ODS) and measured by amperometric detection using an electrochemical detector (Waters, mod 460, Milford, Massachusetts). Correlation coefficient and detection limit of this method were respectively 0.992 and 0.08 nmol/l.

### Statistical Analysis

In each animal group, comparison of the recorded variables over time was conducted by a one-way analysis of variance for repeated measurements followed by a Duncan's multiple comparisons test; comparisons between both animal groups were made using an unpaired Student's *t* test. For all statistical comparisons, differences were considered significant if $P < 0.05$.

## Results

In a preliminary study, we determined the pharmacokinetic parameters of a 2 mg iv bolus of atracurium in five pigs: maximal plasma concentration of atracurium measured at time 0 (time of administration of atracurium) was 16.74 ± 1.70 μg/ml (mean ± SE), plasma elimination half-life was 28.6 ± 6.3 min, volume of distribution was 383 ± 57 ml/kg, and total plasma clearance was 9.7 ± 2.0 ml · min$^{-1}$ · kg$^{-1}$ (table 1).

Rectal temperature was maintained in a narrow range during the whole experimentation in the control group (36.4 ± 0.4° C) and during the three phases of liver transplantation in the experimental group (before liver exclusion: 35.9 ± 0.3° C; during cross clamping: 36.6 ± 0.6° C; after liver recirculation: 36.2 ± 0.5° C). Similarly, arterial *p*H remained stable in both animal groups during the entire study (control group: 7.42 ± 0.01; experimental group during the three reported phases: 7.46 ± 0.01, 7.37 ± 0.02, and 7.36 ± 0.02, respectively).

Systemic hemodynamic values in the control group remained within 20% of baseline values during the entire investigation and are reported in table 2. Hemodynamic variables of the experimental group are also reported in table 2. Systemic mean arterial pressure and central venous pressure did not significantly change during the three phases of liver transplantation. In contrast, trans-

TABLE 2. Hemodynamic Variables, $Pa_{CO_2}$, Arterial *p*H, and Rectal Temperature in Transplanted and Control Animals

| | Transplanted Animals (n = 9) | | | Controls (n = 3) |
|---|---|---|---|---|
| | Before clamping of liver vessels | Anhepatic phase | After recirculation of the liver | |
| Duration (min) | 90 ± 7 | 90 ± 5 | 120 ± 10 | 240 |
| HR (beats per min) | 131 ± 7 | 165 ± 5* | 149 ± 4* | 128 ± 7 |
| MAP (mmHg) | 83 ± 3 | 79 ± 4 | 74 ± 5 | 80 ± 3 |
| CVP (mmHg) | 2 ± 1 | 2 ± 1 | 3 ± 1 | 2 ± 1 |
| $Pa_{CO_2}$ (mmHg) | 34 ± 1 | 35 ± 1 | 36 ± 1 | 35 ± 1 |
| Arterial *p*H (U) | 7.46 ± 0.01 | 7.37 ± 0.02* | 7.36 ± 0.02* | 7.42 ± 0.01 |
| Rectal temperature (°C) | 35.9 ± 0.3 | 36.6 ± 0.6 | 36.2 ± 0.3 | 36.4 ± 0.4 |

HR: heart rate; MAP: mean systemic arterial pressure; CVP: central venous pressure × ± SE: mean of data collected every 15 min in each animal of both groups. No statistical difference between control group and the period before crossclamping of liver vessels.
* $P < 0.05$ from before crossclamping of liver vessels.

planted animals developed a significant tachycardia during the anhepatic phase of liver transplantation (165 ± 5 *vs.* 131 ± 5 beats per min), which was maintained after recirculation of the liver.

Figure 1 shows plasma concentrations of atracurium and laudanosine of the control group over time. Plasma concentrations of atracurium remained stable between 6.5–8.0 μg/ml during the 240-min duration of the constant rate atracurium infusion. Plasma concentrations of laudanosine increased during the first 60 min of the study, then remained stable between 0.69–0.74 μg/ml up to the end of the experiment.

Figure 2 shows plasma concentrations of atracurium and laudanosine during the three different phases of liver transplantation. Plasma concentrations of atracurium remained stable between 10–12 μg/ml during the entire investigation, whatever the function of the liver. In contrast, plasma concentrations of laudanosine increased significantly 45 min after the hepatic vessels were clamped (from 0.57 ± 0.03 μg/ml to 0.91 ± 0.02 μg/ml, $P < 0.05$), reached 1.24 ± 0.05 μg/ml to 90 min after the vessels were clamped, and remained at these elevated concentrations after restoration of circulation to the transplanted liver.

In control animals, plasma norepinephrine concentrations remained stable between 6.5 ± 1.4 (lowest) and 7.6 ± 1.3 nmol/l (highest) during the 240-min duration of the study period. In animals undergoing transplantation, plasma norepinephrine concentrations were significantly increased after the clamping of liver vessels (from 7.8 ± 1.2 to 14.1 ± 2.2 nmol/l, $P < 0.05$) and remained at these elevated concentrations after restoration of liver circulation (18.7 ± 2.90 nmol/l, $P < 0.05$). Figure 3 shows that the increases in norepinephrine concentrations significantly correlated with simultaneous increases in laudanosine plasma concentrations ($r = 0.66$, $P < 0.001$).

Atracurium-induced neuromuscular blockade remained stable between 90–95% (90–95% depression of the precurarization twitch height) in each animal of both groups during the entire experiment. In particular, clamping of liver vessels or recirculation in the liver did not significantly modify the neuromuscular blockade induced by the constant-rate iv atracurium infusion of 120 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

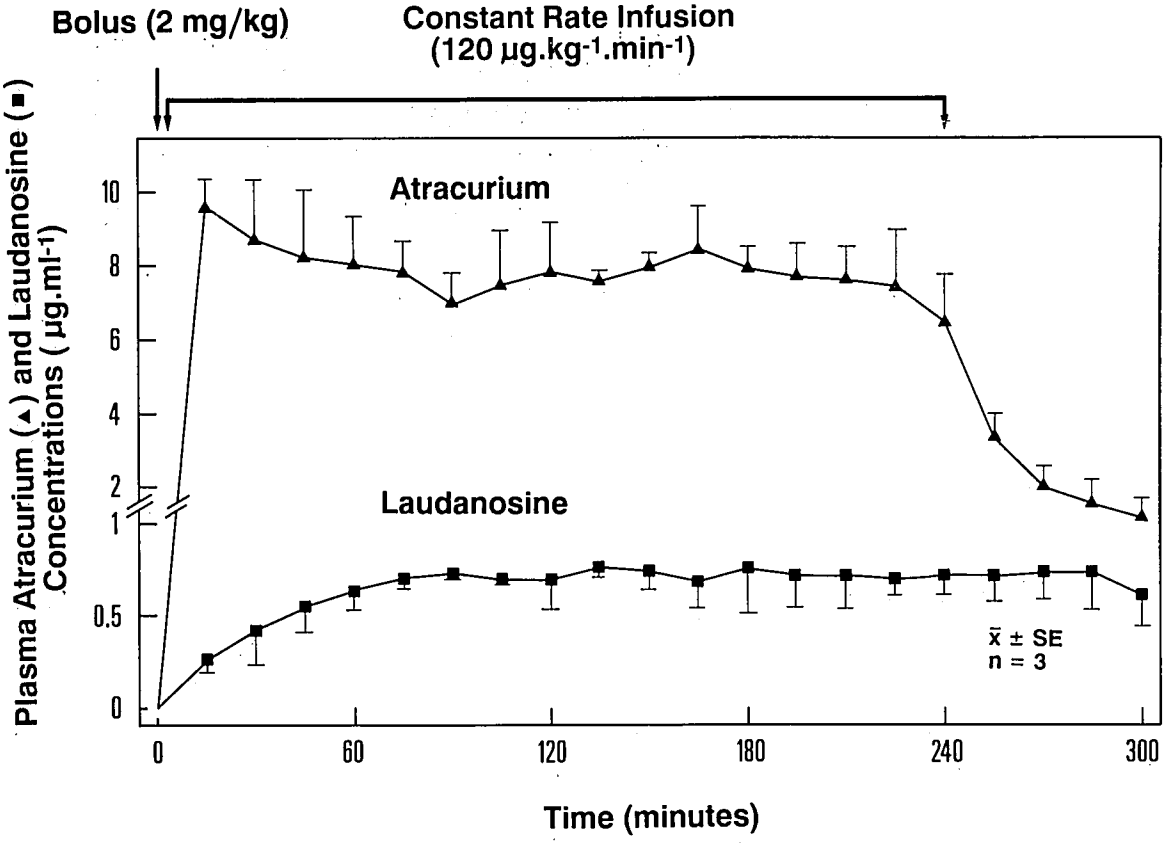


FIG. 1. Plasma concentrations of atracurium (▲) and laudanosine (■) during a 240-min constant-rate iv infusion of atracurium (120 $\mu g \cdot kg^{-1} \cdot min^{-1}$) in control pigs. Data points represent mean ± SE values of three animals taken every 15 min.

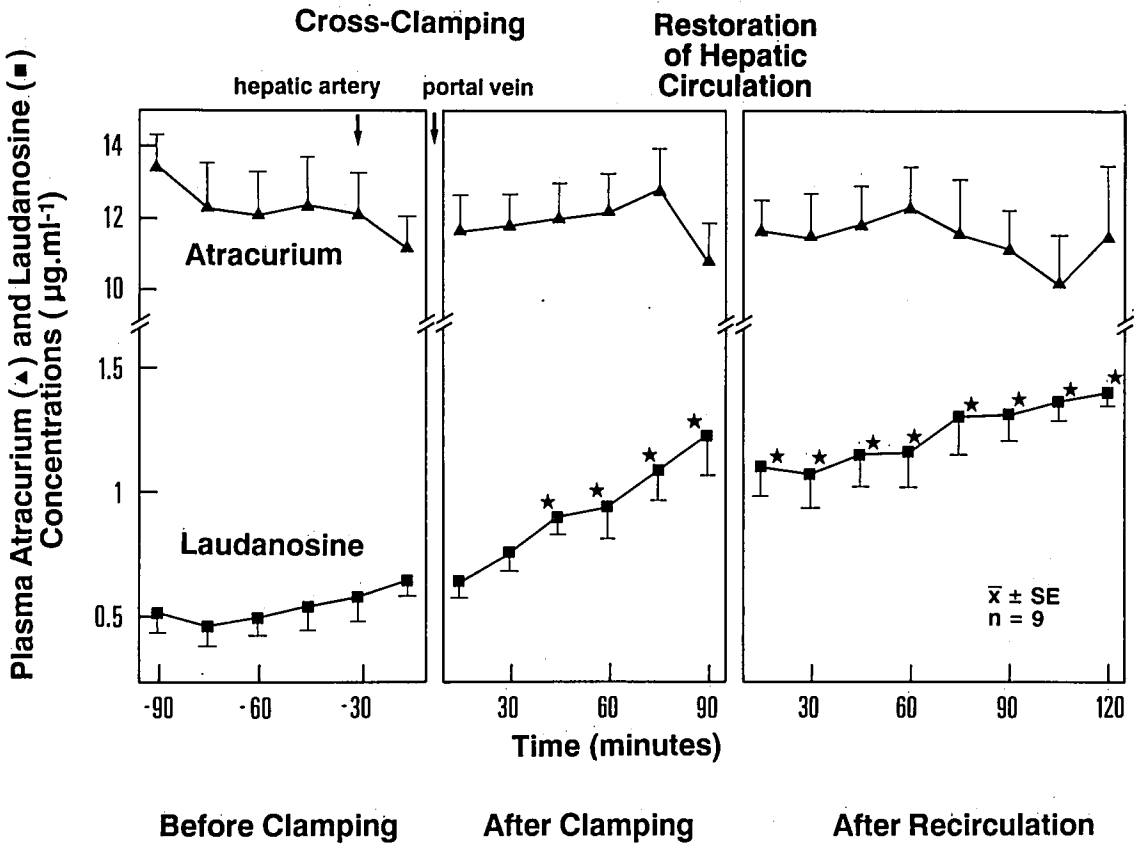


FIG. 2. Plasma concentrations of atracurium (▲) and laudanosine (■) during the three phases of orthotopic liver transplantation in pigs. Data points represent mean ± SE values of nine animals taken every 15 min. *Significantly different ($P < 0.05$) from baseline values, *i.e.*, 15 min before the hepatic vessels were clamped.

## Discussion

The results of the present study show that plasma concentrations and the neuromuscular effect of atracurium are not influenced by the absence of hepatic function and circulation during orthotopic liver transplantation in pigs. This indicates that the liver does not play an important role in plasma clearance of atracurium in pigs. In contrast, plasma laudanosine concentrations increased more than twofold after cross clamping of the portal vein, indicating that, in contrast to atracurium, laudanosine metabolism and elimination are strongly influenced by liver function in pigs.

The previously described HPLC techniques used to measure plasma concentrations of atracurium and laudanosine[8,9] require the use of a gradient solvent elution and have to maintain the column at 60° C during the whole measurement. Temperature of the column has to be maintained in a very narrow range to obtain a good reproducibility of the results. We have developed a simplified method that can be performed at room temperature, by modifying acidity and salt concentration of the solvent. This modification allows to use an isocratic solvent medium. Despite the modification of the method, detection limits of both substances are as low as those reported with other techniques.[8,9]

In the present study, pigs were used to quantify the changes in plasma concentrations of atracurium and laudanosine induced by the lack of hepatic function during liver transplantation. The cat is the classical animal used to study new nondepolarizing muscle relaxants, and to predict their potency and cardiovascular side effects in humans.[10] However, the cat has proved to be of little value to predict the duration of action of NM blocking agents in humans.[11] Since the pig and the human liver have similar enzyme systems,[12] the pig has recently been suggested as an appropriate animal in which to study the effects of muscle relaxants.[13] Preliminary results suggest that it provides more reliable time course data for NM blocking agents than does the cat.[13,14] Indeed, Muir and Marshall found that the time course and potency of three nondepolarizing muscle relaxants in pigs agree well with

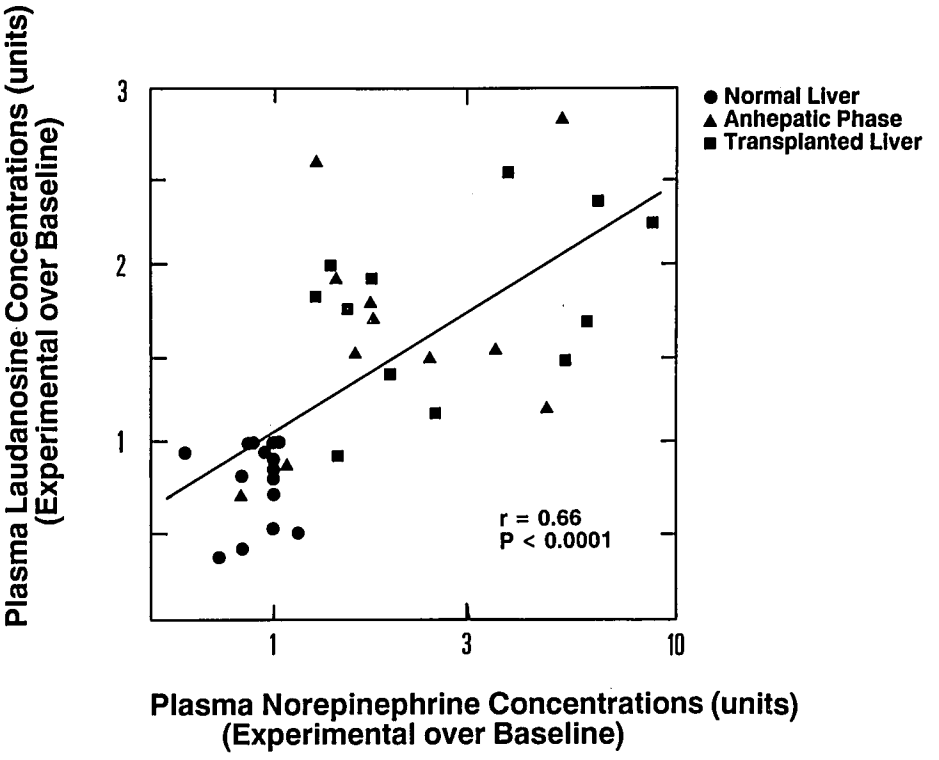


FIG. 3. Correlation between individual changes of plasma norepinephrine and laudanosine concentrations measured before (●), during (▲), and after (■) clamping of liver vessels.

those reported effects in humans.[13] In the present study, we found that the dose of atracurium necessary to produce a 95% twitch depression was approximately eight times greater than that required in humans for a similar NM blockade.[15] An increased $ED_{95}$ of atracurium in pigs (0.9 mg/kg) has also been found by Motsch.*** The iv infusion rate of atracurium necessary to maintain a 90–95% twitch suppression was 20 times greater in pigs than in humans.[16] Despite this difference in pharmacodynamics, the results of our preliminary study demonstrate that pharmacokinetics of an iv bolus of atracurium between pig and humans[17,18] are only slightly different.

Despite the fact that our control animals have not been operated on, we consider them as a true control group. Indeed, it has been reported that in pigs isoflurane anesthesia alone (1 MAC = 1.2%) does not decrease total hepatic blood flow (THBF),[19] and that isoflurane anesthesia (1 MAC) with surgical stress (laparotomy and hepatic dissection) decreases THBF not more than 25% of control values.[20] In the same study, the authors reported that fentanyl anesthesia and surgical stress did not produce any change in THBF. From these results, it would appear that the combination of isoflurane anesthesia (1 MAC) and surgical stress produces only a moderate decrease in THBF. Since we have used a lower concentration of isoflurane (0.5%) with fentanyl, we would only expect a small and probably unimportant decrease in THBF during the first phase of liver transplantation, which has probably not influenced the metabolism of laudanosine. This is confirmed by the fact that values of plasma laudanosine concentration are similar and stable in control animals as well as in experimental pigs during the first phase of liver transplantation (laparotomy and preparation of liver vessels and ligaments to allow hepatectomy).

In control animals, administration of a bolus and a constant-rate iv infusion of atracurium produced a stable plasma concentration of atracurium up to the end of infusion. In animals undergoing transplantation, plasma concentration of atracurium was not significantly modified by exclusion and recirculation of the liver. These results confirm the human studies of Ward[1] and Cook,§§ who did not find a significant difference in the pharmacokinetics of atracurium between healthy patients and those with severe liver dysfunction. Since it is known that the pharmacokinetic profile of atracurium is not significantly affected by the absence of renal function,[21,22] our results confirm the importance of *p*H and temperature-dependent removal of the atracurium molecule from the body (Hofmann elimination) and the role of nonrenal pathways of plasma clearance of atracurium.[23]

The degree of atracurium-induced neuromuscular

*** Personal communication.

blockade was stable during the constant iv infusion rate in every animal of both groups. These results did not confirm the work of Tsai *et al.*, who reported a prolonged pharmacodynamic effect of atracurium after clamping the liver vessels in primates.[2] However, these authors did not measure plasma concentrations of atracurium. The discrepancy between this study and our results can be explained by the hypothesis that the plasma concentration of atracurium did not remain stable after clamping of liver vessels in primates. In that experiment, the splanchnic circulation was not drained by an extracorporeal bypass during the clamping of liver vessels. This can produce an important blood pooling in the splanchnic area and change plasma concentration of atracurium. In humans, Farman and colleagues also reported a prolonged pharmacodynamic effect of atracurium during the anhepatic phase of liver transplantation.[3] Atracurium plasma concentrations were not determined in their study and all patients presented during the anhepatic phase a significant metabolic acidosis and a significant decrease of rectal temperature, both of which can reduce plasma clearance of atracurium by reducing the rate of Hofmann elimination.[24-26]

In control animals, plasma concentrations of laudanosine increased only during the first 60 min after the start of the iv infusion of atracurium, then remained stable until the end of the study. In animals undergoing transplantation, laudanosine plasma concentrations measured before exclusion of the hepatic circulation were similar to those measured in control animals. Clamping of the hepatic vessels produced within 90 min a significant rise (220% of baseline) in laudanosine plasma concentrations in animals undergoing transplantation. These results confirm the human studies of Vine *et al.*,[27] and Ward and Weatherley,[28] who found a significant increase in the elimination half-life of laudanosine in patients with severe liver dysfunction. Our results suggest that the liver is also the most important route of elimination for laudanosine in pigs. Similarly, it has been shown in anesthetized cats that the excretion of laudanosine is 70% biliary and 30% urinary.[29] In contrast, the kidney has a greater role than the liver in the excretion of laudanosine in dogs.[30] After restoration of the hepatic circulation, laudanosine plasma concentrations remained elevated for 120 min (until the end of the procedure). This fact can be explained by the long elimination half-life of laudanosine[28] and the decreased function of the hepatic graft immediately after transplantation.[31]

There was a significant correlation between the increase in plasma concentrations of laudanosine and norepinephrine during the anhepatic phase of liver transplantation. This close relationship could be explained by a release of norepinephrine induced by laudanosine, as demonstrated *in vitro* by Nagashima on guinea pig atrial tissues.¶¶ Another likely explanation for this increase in norepinephrine concentrations is a reduced level of anesthesia, due to a decrease in the anesthetic potency of volatile agents induced by laudanosine.[30,32] Indeed, all animals undergoing transplantation developed a significant tachycardia during the anhepatic phase, which was not associated with a change in central venous pressure. Moreover, we did not observe this tachycardia during liver transplantation in the same animal model using another muscle relaxant.[33]

In conclusion, the results of the present study demonstrate that in pigs plasma clearance of atracurium is not dependent on hepatic function. In contrast, plasma clearance of its major metabolite, laudanosine, is strongly dependent on liver function. This fact cannot be neglected when using atracurium over a prolonged period in patients with severe liver dysfunction.

The authors wish to thank Dr. R. Hughes of The Wellcome Foundation Ltd. for supplying atracurium and laudanosine used for the determination of plasma concentrations of atracurium and laudanosine in this study, and Mrs. Michèle Brunet for her technical assistance.

## References

1. Ward S, Neill EA: Pharmacokinetics of atracurium in acute hepatic failure (with acute renal failure). Br J Anaesth 55:1169–1172, 1983
2. Tsai SK, Lee C, Mok MS: Atracurium induced neuromuscular block is prolonged in hepatic vascular occlusion (abstract). ANESTHESIOLOGY 67:A605, 1987
3. Farman JV, Turner JM, Blanloeil Y: Atracurium in liver transplantation. Br J Anaesth 58:98S–102S, 1986
4. Canfell PC, Castagnoli N, Fahey M, Hennis PJ, Miller RD. The metabolic disposition of laudanosine in dog, rabbit, and man. Drug Metab Disp 14:703–708, 1986
5. Ingram MD, Sclabassi RJ, Cook DR, Stiller RL, Benett MH: Cardiovascular and electroencephalographic effects of laudanosine in "nephrectomized" cats. Br J Anaesth 58:14S–19S, 1986
6. Yate PM, Flynn PJ, Arnold RW, Weatherley BC, Simmonds RJ, Dopson T: Clinical experience and plasma laudanosine concentrations during the infusion of atracurium in the intensive therapy unit. Br J Anaesth 59:211–217, 1987
7. Ward S, Neill EAM, Weatherley BC, Corall JM: Pharmacokinetics of atracurium besylate in healthy patients (after a single i.v. bolus dose). Br J Anaesth 55:213–218, 1983
8. Simmonds RJ: Determination of atracurium, laudanosine and related compounds in plasma by high performance liquid chromatography. J Chromatogr 343:431–436, 1985
9. Neill EAM, Jones CR: The determination of atracurium besylate in human plasma. J Chromatogr 274:409–411, 1983
10. Hughes R: Experimental and clinical evaluation of neuromuscular blocking agents. J Pharmacol Methods 12:1–27, 1984
11. Agoston S, Houvertjes MC, Salt PJ: A new method for studying the relationship between hepatic uptake of drugs and their pharmacodynamic effects in anesthetized cats. Br J Pharmacol 68:637–643, 1980
12. Short CR, Smith RD: Perinatal development of hepatic microsomal mixed function oxidase activity in swine. Biochem Pharmacol 22:1309–1319, 1973

13. Muir AW, Marshall RJ: Comparative neuromuscular blocking effects of vecuronium, pancuronium, ORG 6368 and suxamethonium in the anaesthetized domestic pig. Br J Anaesth 59: 622–629, 1987
14. Motsch J, Hennis PJ, Zimmermann FA, Agoston S: A model for determining the influence of hepatic uptake of nondepolarizing muscle relaxants in the pig. ANESTHESIOLOGY 70:128–133, 1989
15. Basta SJ, Ali HH, Savarese JJ, Sunder N, Gionfriddo M, Cloutier G, Linberry C, Cato AE: Clinical pharmacology of atracurium besylate (BW33A): A new non-depolarizing muscle relaxant. Anesth Analg 61:723–729, 1982
16. Eagar, Flynn D, Hughes R: Infusion of atracurium for long surgical procedures. Br J Anaesth 56:447–453, 1984
17. Hughes R, Chapple DJ: The pharmacology of atracurium: A new competitive neuromuscular blocking agent. Br J Anaesth 52: 31–44, 1981
18. Parker CJR, Hunter JM: Pharmacokinetics of atracurium and laudanosine in patients with hepatic cirrhosis. Br J Anaesth 62: 177–183, 1989
19. Lundeen G, Manohar M, Parks C: Systemic distribution of blood flow in swine while awake and during 1.0 and 1.5 MAC isoflurane anesthesia with and without 50% nitrous oxide: Anesth Analg 62:499–512, 1983
20. Gelman S, Dillard E, Bradley EL: Hepatic circulation during surgical stress and anesthesia with halothane, isoflurane, or fentanyl. Anesth Analg 66:936–943, 1987
21. Ward S, Boheimer N, Weatherley BC, Simmonds RJ, Dopson TA: Pharmacokinetics of atracurium and its metabolites in patients with normal renal function, and in patients in renal failure. Br J Anaesth 59:697–706, 1987
22. Fahey M, Rupp SM, Fisher DM, Miller RD, Sharma M, Canfell C, Castagnoli K, Hennis P: The pharmacokinetics and pharmacodynamics of atracurium in patients with and without renal failure. ANESTHESIOLOGY 61:699–702, 1984
23. Fisher DM, Canfell PC, Fahey MR, Rosen JI, Rupp SM, Sheiner LB, Miller R. Elimination of atracurium in humans: Contribution of Hofmann elimination and ester hydrolysis versus organ-based elimination. ANESTHESIOLOGY 65:6–12, 1986
24. Stenlake JB, Waigh RD, Urwin J, Dewar GH, Coker JJ: Atracurium. Conception and inception. Br J Anaesth 55:3S–10S, 1983
25. Hofmann AW: Beiträge zur Kenntniss der flüchtigen organischen Basen. Ann Chem 78:252–258, 1851
26. Flynn PJ, Hughes R, Walton B, Jothilingham S: Use of atracurium infusions for general surgical procedures including cardiac surgery with induced hypothermia. Br J Anaesth 55:135S–138S, 1983
27. Vine P, Boheimer N, Ward S, Wheatherley B, Buick A, Smith I: Laudanosine pharmacokinetics after bolus atracurium in patients with hepato-biliary dysfunction. Br J Anaesth [Suppl] 58:1327S, 1986
28. Ward S, Weatherley BC: Pharmacokinetics of atracurium and its metabolites. Br J Anaesth [Suppl] 58:6S–10S, 1986
29. Neill EAM, Capple DJ: Metabolic studies in the cat with atracurium: A new neuromuscular blocking agent designed for non-enzymic inactivation at physiological pH. Xenobiotica 12:203–210, 1982
30. Hennis PJ, Fahey MR, Canfell PC, Wei-zhong Shi, RD Miller. Pharmacology of laudanosine in dogs. ANESTHESIOLOGY 65: 56–60, 1986
31. Marsh J, Gordon RD, Stieber A, Starzl TE: Critical care of the liver transplant patient, Textbook of Critical Care. Edited by Shoemaker WC, Thompson WL, Holbrook PR. Philadelphia, W. B. Saunders Co, 1987 pp 1329–1333
32. Wei-zhong S, Fahey M, Fisher DM, Miller RD, Canfell C, Eger II EI: Laudanosine (a metabolite of atracurium) increases the minimum alveolar concentration of halothane in rabbits. ANESTHESIOLOGY 63:584–588, 1985
33. Pittet JF, Tassonyi E, Schopfer C, Morel DR, Fathi M, Benakis A: Elevated plasma levels of laudanosine are associated with high plasma concentrations of norepinephrine during orthotopic liver transplantation in pigs (abstract). ANESTHESIOLOGY 69: A484, 1988