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Pharmacokinetics and Pharmacodynamics of Vecuronium in Rats with Systemic Inflammatory Response Syndrome

Treatment with N^G*-Monomethyl-L-Arginine*

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Background: **Insufficient detoxification caused by nitric oxide—related inhibition of cytochrome P450 may be important for metabolism of numerous drugs, including vecuronium. The present study investigated the pharmacodynamics and pharmacokinetics of vecuronium in rats with inflammatory liver dysfunction.**

Methods: **Male Sprague–Dawley rats (n = 56) were randomly allocated into two groups: In the sepsis group, liver inflammation was established by injection of 56 mg/kg heat-killed *Corynebacterium parvum;* control rats received the solvent. At day 4, groups were subdivided according to treatment with the nitric oxide synthase inhibitor N^G-monomethyl-L-arginine (250 mg/kg) or placebo. The aminopyrine breath test was performed to assess cytochrome P450 activity. Rats were anesthetized with propofol and mechanically ventilated. Duration of action of vecuronium (1.2 mg/kg) was measured by evoked mechanomyography (stimulation of the sciatic nerve, contraction of the gastrocnemius muscle). In seven rats of each subgroup a 50% neuromuscular blockade was established by a continuous vecuronium infusion. Vecuronium plasma levels were measured and plasma clearance of vecuronium was calculated. Nitric oxide synthesis was assessed by measuring nitrite/nitrate serum levels.**

Results: **In sepsis/placebo rats, vecuronium-induced neuromuscular blockade was prolonged (144% of control/placebo), vecuronium plasma levels at 50% neuromuscular blockade were increased (122% of control/placebo), and plasma clearance was decreased (68% of control/placebo). N^G-monomethyl-L-arginine therapy in rats with sepsis improved cytochrome P450 activity and plasma clearance of vecuronium, shortened duration of action of vecuronium, but did not alter the elevated vecuronium plasma levels.**

Conclusions: **A systemic inflammatory response syndrome with liver dysfunction results in decreased sensitivity to and a decreased elimination of vecuronium. Modulation of nitric oxide synthesis may be a strategy that can be used in the future to improve xenobiotic metabolism in sepsis. (Key words: Cytochrome P450; neuromuscular blocking agent; nitric oxide; sepsis.)**

INSUFFICIENT detoxification of numerous drugs is a serious problem in the management of hepatic failure associated with a systemic inflammatory response syndrome.[1] Some steps in the pathogenesis of this process have been characterized, demonstrating an important role for nitric oxide (NO) biosynthesis.

Exogenously applied NO[2] as well as endogenously produced NO[3] suppresses activity of cytochrome P450 enzymes, which are key enzymes of xenobiosis. *In vivo* stimulation of inducible NO synthase (iNOS) results in a downregulation of cytochrome P450 activity.[4] In a pre-

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vious *in vivo* experiment we demonstrated the effect of iNOS induction on the cytochrome P450–dependent detoxification using the aminopyrine breath test. Inhibition of iNOS 4 days after administration of the inflammatory stimulus resulted in a restitution of cytochrome P450 activity.[5] However, the clinical relevance of these findings remained unclear.

Pittet *et al.*[6] demonstrated a close correlation between the aminopyrine breath test and the speed of neuromuscular recovery following vecuronium administration in pigs after liver transplantation. If a similar effect occurs during inflammatory hepatic dysfunction, iNOS inhibition might prove to be a viable therapeutic option to restore P450 function.

Thus, the aim of this study was to investigate the effect of iNOS induction and its inhibition on drug metabolism by means of the pharmacokinetics and pharmacodynamics of vecuronium, using a rat model of inflammatory liver dysfunction.

Methods

Animal Model

Fifty-six male Sprague–Dawley rats (Charles River GmbH, Kisslegg, Germany), 250–350 g, were allowed to accommodate to standard conditions with free access to chow and water for 14 days. The rats were randomly assigned to two groups according to the experimental model of granulomatous liver inflammation and its therapy with N^G-monomethyl-L-arginine (NMA).[5] In rats of one group (n = 28), 56 mg/kg heat-killed *Corynebacterium parvum* (Universal Biologicals, London, UK) was intravenously injected in total volume of 0.5 ml saline. Rats of the control group (n = 28) received the equivalent volume of saline. Four days later, each group was further divided into subgroups (n = 14) receiving two intravenous injections of either 125 mg/kg NMA (Clinalpha AG, Läufelfingen, Switzerland) in 0.5 ml saline or placebo (0.5 ml saline) 12 and 9 h before the measurements. This design resulted in four groups of rats: rats without infection not receiving NMA therapy (control/placebo: n = 14), rats without infection receiving NMA therapy (control/NMA: n = 14), infected rats not receiving NMA therapy (sepsis/placebo: n = 14), and infected rats receiving NMA therapy (sepsis/NMA: n = 14). To exclude variances in liver function caused by differences in food intake, rats were fasted beginning 12 h before the measurements.

Aminopyrine Breath Test

Three hours after the second NMA or placebo injection, cytochrome P450 enzyme activity was assessed using the aminopyrine breath test based on the formation of [^{14}C]carbon dioxide from [^{14}C]dimethyl-aminopyrine *via* cytochrome P450–dependent *N*-demethylation.[5] The aminopyrine breath test was started by intravenous injection of [^{14}C]dimethyl-aminopyrine (Amersham International, Braunschweig, Germany) with a specific activity of 57 MBq/kg in 0.5 ml saline. The animals were then placed into a gas-tight tubing with a continuous airflow of 0.7 l/min. The outflow was conducted through a solution of 0.5 M hyaminehydrochloride–alcohol (1:1; v/v; Zinsser Analytic, Frankfurt/Main, Germany) to bind expired CO_2. In the animal model used in this experiment, the maximum [^{14}C]dimethyl-aminopyrine turnover was found to be between 20 and 30 min after injection.[5] Therefore, a vial containing hyamine was placed into the outflow of the gas tubing for this period, and the amount of exhaled [^{14}C]carbon dioxide was determined by the use of a β-counter. The values were expressed as percentages of the totally applied radioactivity, making the test independent from total body CO_2 production.

Anesthesia and Vital Parameters

Anesthesia was induced by inhalation of 4% isoflurane in 100% oxygen and maintained with 2% isoflurane in oxygen *via* head mask in spontaneously breathing animals. Following tracheotomy, mechanical ventilation was continued with oxygen in air (inspired oxygen fraction = 0.4) and adjusted to maintain an end-tidal carbon dioxide partial pressure between 32 mmHg and 36 mmHg. After cannulation of the left external jugular vein, anesthesia was switched to a continuous infusion of propofol (20–40 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}) and maintained according to cardiovascular signs of inadequate anesthesia. The left carotid artery was cannulated to measure mean arterial pressure and perform blood gas analyses.

After tracheotomy and cannulation, all animals were allowed to equilibrate over a period of 15 min, after which baseline recordings of heart rate, mean arterial pressure, rectal temperature, and base excess were performed. Afterward, hypovolemia, if present, was treated with hydroxyethyl starch (6%; 450/0.7) to establish a central venous pressure between 6 and 8 mmHg. The amount of necessary hydroxyethyl starch was documented. Following hydroxyethyl starch administration, mean arterial pressure ranged between 80 and 90 mmHg

and was stable in each animal during the neuromuscular function tests.

Prior to the neuromuscular experiments ventilation was adjusted to maintain an arterial carbon dioxide partial pressure between 36 and 40 mmHg. Base excess was corrected with 1 mM sodium bicarbonate to values between 3 mM and −3 mM. Arterial oxygen partial pressure and concentration of ionized calcium were kept within normal limits, and rectal temperature was controlled between 36.5 and 37.5°C with warming blankets.

Neuromuscular Function

The sciatic nerve of the immobilized leg was exposed at its exit from the lumbosacral plexus. The ankle joint was fixated and a force transducer connected to the foot at a right angle. Stimulation of the sciatic nerve was done by train-of-four stimuli every 12 s. The contraction of the gastrocnemius muscle was measured by evoked mechanomyography (Myograph, Biometer, Copenhagen, Denmark). Supramaximal stimulus and control twitch height (T_0) were established. Baseline mechanomyographic response was stabilized over a period of 10 min before injection of a fourfold ED_{95} of vecuronium (1.2 mg/kg; n = 14). In a preliminary investigation we had evaluated the ED_{95} of vecuronium in five nonseptic and untreated rats using the same preparation. After the bolus injection, neuromuscular transmission was allowed to recover to baseline values. The intervals between injection of vecuronium and the recovery of the first twitch (T_1) to 25% (duration 25% [seconds]) and 75% (duration 75% [seconds]) were measured. The recovery interval was calculated by: recovery interval [seconds] = duration 75% − duration 25%. In the first seven animals of each group the *in vivo* experiment was terminated at this step. In the second seven animals of each group a continuous infusion of vecuronium was adjusted to achieve a constant T_1/T_0 of 50%. Following 10 min of stable T_1/T_0 = 50%, steady state conditions were assumed. The required infusion rates were documented, and 2 ml of heparinized blood was withdrawn for vecuronium plasma level determination. The withdrawn blood was centrifuged (3,500 rpm, 10 min, 4°C), the supernatant removed, and the equipotent amount of phosphate buffer added to the plasma. The samples were immediately frozen at −70°C. Following this, animals were killed by exsanguination. Plasma was separated by centrifugation and immediately stored at −70°C.

Chemical Analyses

Nitric oxide synthesis was assessed by measuring levels of serum nitrite and nitrate, which are the stable products of NO oxidation. Plasma samples were deproteinized with 0.5 M NaOH and 10% $ZnSO_4$. Nitrate was then converted to nitrite using high-performance liquid chromatography on a cadmium column. Nitrite concentrations were determined spectrophotometrically at 540 nm using a method based on the Griess reaction.[7] The activity of the glutamate pyruvate transaminase (GPT) was measured with an automatic procedure at the Institute of Clinical Chemistry, Technische Universität München. Vecuronium plasma levels were analyzed by a high-performance liquid chromatography–tandem mass spectrometry at the Institute of Clinical Chemistry, University Hospital, Zürich, Switzerland. Plasma clearance of vecuronium during steady state conditions was calculated by the equation: clearance = infusion rate/plasma level.

Statistical Analyses

Data are given as means ± SD. Statistical analyses were performed using factorial analysis of variance. *Post hoc* analysis was performed in four of six possible comparisons by the Dunnett *t* test, according to the objectives: autonomic effect of NMA (control/placebo *vs.* control/NMA), effect of infection (control/placebo *vs.* sepsis/placebo), effect of NMA therapy in infected rats compared with control rats (sepsis/NMA *vs.* control/placebo), and effect of NMA therapy in infected rats compared with sick rats (sepsis/NMA *vs.* sepsis/placebo). Differences were considered significant at $P < 0.05$.

Regressions were calculated between the aminopyrine breath test and the recovery interval of vecuronium as well as between the aminopyrine breath test and the vecuronium clearance during steady state conditions at 50% neuromuscular blockade. Correlations were calculated by linear least-squares regressions.

Results

Systemic Signs

To analyze systemic symptoms of inflammation, body weights of the animals were compared at day 4, prior to the first NMA or placebo injection. All control rats (control/placebo and control/NMA) gained weight (8 ± 5 g); all rats with corynebacterium parvum injections (sepsis/placebo and sepsis/NMA) showed a significant loss of body weight (−5 ± 8 g).

Table 1. Nitrite Plus Nitrate Serum Concentrations, Aminopyrine Breath Test, and Liver Enzyme Release

	Control/ Placebo	Control/ NMA	Sepsis/ Placebo	Sepsis/ NMA
Nitrite + nitrate (M/l)	40 ± 11	27 ± 6	1157 ± 636	112 ± 67†‡
ABT (%)	3.2 ± 1.3	3.4 ± 0.7	1.3 ± 0.6	2.2 ± 0.6*†‡
GPT (U/l)	30 ± 2	27 ± 5	55 ± 20	56 ± 28†‡

Values are means ± SD, n = 14 per group.

ABT = aminopyrine breath test; GPT = glutamate pyruvate transaminase.

$P < 0.05$: *control/placebo *vs.* sepsis/placebo (effect of infection); †sepsis/NMA *vs.* control/placebo (effect of NMA therapy compared with control rats); ‡sepsis/NMA *vs.* sepsis/placebo (effect of NMA therapy compared with sick rats).

Vital parameters were evaluated after induction of anesthesia and cannulation of venous and arterial vessels. No differences between groups were found regarding mean arterial pressure (75–130 mmHg), heart rate (295–390 beats/min), base excess (−5.1–3.1 mM), or rectal temperature (34.1–37.9°C). The amount of hydroxyethyl starch necessary to increase the central venous pressure to 6–8 mmHg was significantly higher in both groups injected with *Corynebacterium parvum* (sepsis/placebo and sepsis/NMA: 2.1 ± 1.4 ml) compared with control animals (control/placebo and control/NMA: 5.1 ± 1.1 ml).

Quantification of Cytochrome P450 Activity, NO Production, and GPT

The aminopyrine turnover in sepsis/placebo rats was suppressed to 41% of that of control/placebo rats. Treatment with NMA significantly improved the aminopyrine turnover in the sepsis/NMA group (69% of control/placebo). Sepsis/placebo rats had extremely elevated nitrite/nitrate serum levels compared with control/placebo rats. Sepsis/NMA rats had significantly lower nitrite/nitrate serum concentrations compared with sepsis/placebo rats. Injection of *Corynebacterium parvum* was followed by elevated GPT levels. Treatment with NMA did not significantly affect GPT levels in either the control group or animals injected with *Corynebacterium parvum* (table 1).

Vecuronium-induced Neuromuscular Blockade

Vecuronium-induced neuromuscular blockade (as measured by duration 25%, duration 75%, and recovery interval) was prolonged in sepsis/placebo rats compared with control/placebo rats. Sepsis/NMA rats had duration 25%, duration 75% and recovery interval comparable to control/placebo rats (table 2).

Table 2. Neuromuscular Block Induced by 1.2 mg/kg Vecuronium ($4 \times ED_{95}$)

	Control/ Placebo	Control/ NMA	Sepsis/ Placebo	Sepsis/ NMA
Duration 25% (s)	389 ± 85	445 ± 75	532 ± 122	373 ± 90*†
Duration 75% (s)	479 ± 125	563 ± 99	692 ± 137	453 ± 125*†
Recovery index (s)	90 ± 46	118 ± 36	168 ± 52	94 ± 42*†

Values are means ± SD; n = 14 per group.

$P < 0.05$: *control/placebo *vs.* sepsis/placebo (effect of infection); †sepsis/NMA *vs.* sepsis/placebo (effect of NMA therapy compared with sick rats).

Sepsis/placebo rats had significantly higher plasma levels of vecuronium compared with control/placebo rats. This significance was maintained between control/placebo rats with sepsis/NMA rats (table 3). Infusion rate and plasma clearance were significantly decreased in sepsis/placebo rats compared with control/placebo rats. Treatment of the sepsis group with NMA resulted in an increased infusion rate and plasma clearance compared with the sepsis/placebo group (table 3).

Comparison of the regression analysis of the vecuronium plasma clearance and recovery index with the aminopyrine breath test showed that the vecuronium plasma clearance correlated better with the aminopyrine breath test (r = 0.707) than the recovery index (r = 0.447) (figs. 1 and 2).

Discussion

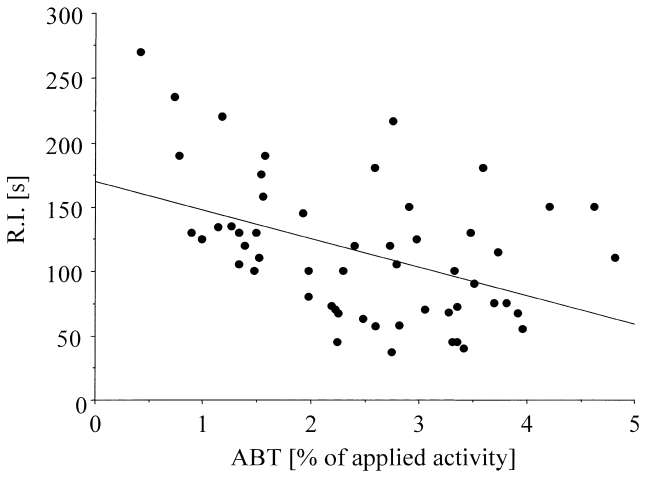
Tremendous progress has been made in understanding the molecular basis of inflammatory response, demon-

Table 3. Vecuronium Plasma Levels, Infusion Rate, and Plasma Clearance of Vecuronium during Steady-state Conditions at a 50% Neuromuscular Blockade

	Control/ Placebo	Control/ NMA	Sepsis/ Placebo	Sepsis/ NMA
Plasma levels (μg/l)	295 ± 75	322 ± 42	366 ± 72	373 ± 45*†
Infusion rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	56 ± 15	60 ± 13	40 ± 11	62 ± 16*‡
Clearance ($ml \cdot kg^{-1} \cdot min^{-1}$)	195 ± 39	188 ± 41	114 ± 41	169 ± 47*‡

Values are means ± SD; n = 7 per group.

$P < 0.05$: *control/placebo *vs.* sepsis/placebo (effect of infection); †sepsis/NMA *vs.* control/placebo (effect of NMA therapy compared with control rats); ‡sepsis/NMA *vs.* sepsis/placebo (effect of NMA therapy compared with sick rats).



R.I. = 170 - 22 × ABT; r = 0.447; n = 56

Fig. 1. Regression between aminopyrine breath test (ABT) and recovery interval (R.I.) after administration of 1.2 mg/kg vecuronium.

strating an important role of NO as a mediator during septic conditions. Besides many other effects, NO inhibits the activity of the iron-containing cytochrome P450.[8] It leads to an oxidation of the iron, which is then released from the protein and becomes inactive.[4,8] Metabolism of drugs depending on cytochrome P450 could therefore be affected by septic conditions.

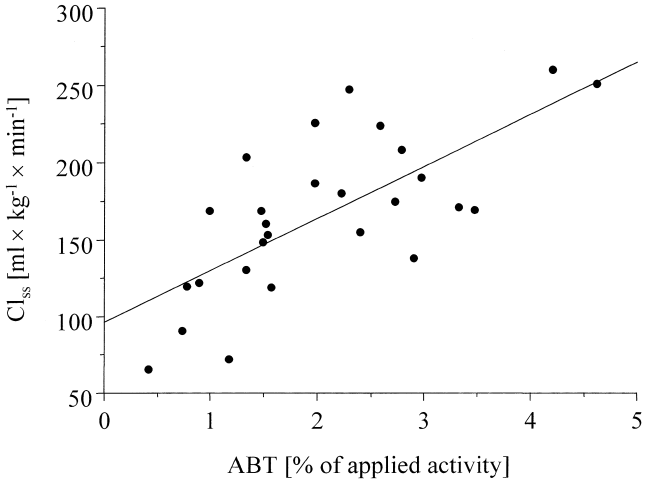
In the rodent model used in the present study, injection of heat-killed *Corynebacterium parvum* causes an induction of the iNOS expression with maximal nitrite/nitrate plasma levels between day 3 and day 6 after injection.[9,10] The NO-induced suppression of the cytochrome P450 activity could be demonstrated with the aminopyrine breath test, reflecting the influence of NO synthesis on the hepatic detoxification processes.[5]

Evidence suggests a role of liver function in the pharmacodynamics of vecuronium.[11] In patients with liver cirrhosis, a reduced plasma clearance has been reported.[12] In addition, reduced infusion rates for the maintenance of a steady state neuromuscular blockade in the anhepatic phase during orthotopic liver transplantation have been described.[13]

In our model of a chronic inflammatory liver dysfunction, the duration of a vecuronium-induced neuromuscular blockade was prolonged, and the plasma clearance for vecuronium was decreased. These findings may be pertinent for clinical practice, because our data prove not only that the pharmacokinetics or metabolism of a diagnostic agent such as aminopyrine are affected by the activity of cytochrome P450, but also that the pharmacodynamic effect of a commonly used drug in clinical practice is altered. An impaired hepatic microsomal metabolism of ethylmorphine and midazolam during sepsis associated with increased NO synthesis has already been described, although without the possibility of monitoring the clinical effects.[14] This dilemma was overcome in our study by using the neuromuscular blocking agent vecuronium. Its clinical effects can be easily measured by neuromuscular monitoring.

Because restitution of cytochrome P450 activity with NMA improves xenobiosis, NMA therapy was expected to shorten the vecuronium induced neuromuscular blockade. However, the normalized duration times and recovery intervals after NMA treatment in rats injected with *Corynebacterium parvum* indicate a normalized drug metabolism, although restitution of cytochrome P450 activity was incomplete. Furthermore, the aminopyrine turnover and the recovery intervals following an injection of 1.2 mg/kg vecuronium did not correlate very well (r = 0.447) in this inflammation model with impaired liver function. In contrast, Pittet *et al.*[6] found a strong correlation (r = 0.843) between aminopyrine turnover and the recovery interval of a vecuronium induced neuromuscular blockade after hepatic autotransplantation in pigs. Therefore, an additional mechanism has to be postulated.

Thus we determined plasma clearance and plasma levels of vecuronium during a 50% neuromuscular blockade in the second seven rats of each group. Plasma clearance



Cl_{ss} = 97 + 34 × ABT; r = 0.707; n = 28

Fig. 2. Regression between aminopyrine breath test (ABT) and plasma clearance (Cl_{ss}) of vecuronium during steady state conditions at a 50% neuromuscular blockade.

of vecuronium during these steady state conditions correlated much better with the aminopyrine turnover ($r = 0.707$) than the recovery intervals. This different finding results from the higher vecuronium plasma levels necessary for 50% neuromuscular blockade, indicating a resistance to vecuronium.

Corresponding results have been reported by Tomera and Martyn,[15] showing a threefold to fivefold rightward shift in the dose–response curves of *d*-tubocurarine 2 weeks after a three-times repeated intraperitoneal injected dose of *Escherichia coli* lipopolysaccharide. They suggested an upregulation of perijunctional immature acetylcholine receptors in sepsis, similar to changes seen in burn injury or muscle disuse atrophy, to be the reason for those results. As additional acetylcholine receptors cause a relative resistance to nondepolarizing neuromuscular blocking drugs,[16] shorter duration of action should be observed in septic rats. Thus, the prolonged duration of the vecuronium-induced neuromuscular blockade demonstrates that the impaired detoxification of vecuronium is the prevailing effect in our model.

The prolongation of the vecuronium-induced neuromuscular blockade and the reduced clearance of vecuronium could also be caused by reduced liver perfusion, which is considered to be one of the major factors in terminating the effect of vecuronium.[17] However, Because NO improves liver perfusion, it is more conceivable that the negative effect of NO on metabolic pathways, *via* inhibition of cytochrome P450 activity, may be counteracted by an improved perfusion. In addition, the effective improvement of the aminopyrine turnover with NMA did not indicate an impaired liver perfusion. Furthermore, GPT activity did not differ between NMA- and placebo-treated animals, regardless of whether they received a *Corynebacterium parvum* injection.

Hepatocellular vecuronium uptake of rats is approximately 10 times higher than that of humans,[18] which leads to a relatively shorter duration of action of vecuronium in rats given vercuronium on an ED_{95}-equivalent base. However, because this study investigated groups with different activities of cytochrome P450, the fact that cytochrome P450 in hepatic microsomes of rats and humans has closely related properties[19] is more relevant for transferability of our results. In addition, the expression of iNOS in human hepatocytes after stimulation with proinflammatory mediators and its effect on human cytochrome P450 is comparable to the situation in rats.[3]

In conclusion, inflammatory liver dysfunction resulted in a decreased sensitivity to and a decreased metabolism of vecuronium. The resistance to vecuronium may be caused by an upregulation of acetylcholine receptors in sepsis. NMA improved vecuronium metabolism as well as aminopyrine turnover in infected rats, indicating a restored drug metabolism. Thus, modulation of NO synthase may be a way to improve xenobiosis in sepsis.

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