Interaction of Rocuronium (ORG 9426) and Phenytoin in a Patient Undergoing Cadaver Renal Transplantation: A Possible Pharmacokinetic Mechanism?

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ROCURONIUM (ORG 9426) is a nondepolarizing neuromuscular blocking drug currently in the final stages of clinical trials. It is a steroidal molecule, is related structurally to vecuronium, and has a rapid onset and an intermediate duration of action.1–3 Phenytoin is an anticonvulsant drug, the chronic administration of which is associated with decreased duration of action and increased dose requirements of nondepolarizing muscle relaxants.4–9 We report the case of a patient undergoing a cadaver renal transplantation in whom the chronic use of phenytoin appeared to be associated with a significant decrease in the duration of a rocuronium-induced neuromuscular block and an increase in rocuronium's plasma clearance.

Case Report

A 28-yr-old, 59-kg man, with an ASA physical status of 3 and end-stage renal disease of unknown origin was admitted for cadaver kidney transplantation. He had been in excellent health until 2 yr before this surgery, when he suffered a generalized tonic-clonic seizure, which lasted about 5 min. The cause of the seizure never was discovered, and he was treated daily with phenytoin (400 mg orally). One year later he developed end-stage renal disease and required hemodialysis. His only other medical problem was hypertension, for which he took the following medications orally: minoxidil (5 mg twice daily), atenolol (50 mg twice daily), captopril (50 mg three times daily), calcium carbonate (650 mg twice daily), and folic acid (1 mg four times daily). At the time of surgery, physical examination revealed the following conditions: an arterial blood pressure of 156/86 mmHg, a heart rate of 72 beats per minute, a systolic murmur of 1/6 without radiation, and a left-upper arm arteriovenous shunt for dialysis. Left ventricular hypertrophy was detected by electrocardiography. He underwent hemodialysis 2 hr before surgery, and preoperative clinical chemistry showed the following concentrations: sodium, 139 mmol·l⁻¹; potassium, 5.2 mmol·l⁻¹; chloride, 101 mmol·l⁻¹; bicarbonate, 30 mmol·l⁻¹; blood urea nitrogen, 18.2 mmol·l⁻¹; and creatinine, 831 µmol·dl⁻¹. The results also showed a white blood cell count of 6.5 × 10⁶ cells·l⁻¹, a hematocrit of 23%, a platelet count of 322 × 10⁶ cells·l⁻¹, a prothrombin time of 11.2 s, and a partial thromboplastin time of 22.2 s.

Because it was not known that the patient was receiving phenytoin, he was enrolled into a study, approved by our Committee on Human Research, investigating the effect of renal failure on the pharmacokinetics of rocuronium. The results of that study have been published but did not include the data for this patient.10 After premedicating the patient with midazolam (2 mg intravenously), we induced anesthesia with thiopental (8.5 mg·kg⁻¹), in divided doses, and fentanyl (5 µg·kg⁻¹), and then gave him inhalational 60% NO₂ in oxygen and 1–5% isoflurane. The patient's trachea was intubated without the administration of a muscle relaxant. Anesthesia was maintained with 60% NO₂ and 0.25–1.0% isoflurane (end-tidal concentrations given were measured by mass spectrometry). Ventilation was controlled to maintain end-tidal Pco₂ between 32 and 42 mmHg, and the esophageal temperature was maintained at 35–37°C. In the first few minutes that followed induction of anesthesia, the patient received ephedrine (5 mg), esmolol (1 g), dexamethasone (120 mg), and atazanavir (240 mg). When reperfusion of the transplanted kidney was performed, at approximately 160 min after induction of anesthesia, we gave the patient dopamine (3 µg·kg⁻¹·min⁻¹), furosemide (80 mg), and mannitol (12.5 g). Intraoperative intravenous fluids consisted of a balanced salt solution (4,000 ml), 5% hydroxyethyl starch (500 ml), and packed red blood cells (1 U) (because of his low preoperative hematocrit).

Anesthesiology, V 80, No 5, May 1994
When the patient's anesthetic conditions and muscle twitch tension (in response to train-of-four stimulation at 2 Hz, repeated at 12-s intervals) were stable, we measured the amplitude of the first twitch in the train-of-four sequence (T1 control) and injected rocuronium (600 μg·kg⁻¹) as an intravenous bolus at 37 min after the induction of anesthesia. Adductor pollicis twitch tension was recorded for 33 min after administration of rocuronium, at which time T1 was 95% and additional muscle relaxation was required for surgical exposure. Thereafter, atracurium (total dose 80 mg), which does not interfere with the assay for rocuronium, was administered. We measured the times from administration of rocuronium until complete ablation of T1 (onset), until the T1 recovered to 25% (clinical duration), and until the control T1 recovered to 90% (relaxation time). Residual neuromuscular block was antagonized with neostigmine (2.0 mg) and glycopyrrolate (0.4 mg) at the end of this 4-h procedure.

Venous blood samples (4-5 ml each) were drawn from the arm, contralateral to the one into which the rocuronium had been injected, before the procedure and at 2, 4, 6, 8, 10, 15, 20, 25, 30, 40, 50, 60, 75, 90, 120, 150, 180, 210, 240, 300, and 360 min after rocuronium administration. Urine was collected for 24 h after rocuronium administration. These samples were analyzed for rocuronium concentration by capillary gas chromatography. In our original paper, we calculated rocuronium pharmacokinetics using a population-based technique (NONMEM). Because this case report focuses on the responses of an individual patient, we present a reanalysis of our original data in which the pharmacokinetic variables of rocuronium are calculated for each individual. The results of this reanalysis pertain to this report only and do not supersede the original population-based analysis. Plasma concentration versus time data were fit to two- and three-compartment pharmacokinetic models using least squares, nonlinear regression, and the more appropriate model was selected in each case. Using standard formulae, we determined total plasma clearance, volume of distribution at steady state, and elimination half-life.

The onset of and recovery from rocuronium-induced block were more rapid in the presence of chronic phenytoin use than in its absence (table 1). Values for relaxation time were obtained from only four of the ten patients who did not receive phenytoin, because the surgical need for muscle relaxation required the administration of atracurium before T1 recovered to 90% in six patients.

A two-compartment model was the more appropriate for the data for the patient receiving phenytoin and for four of the control patients. For the remaining six patients, a three-compartment model was more appropriate. In the patient taking phenytoin, the plasma clearance was greater and the elimination half-life shorter than those for any of the ten other patients (table 1). The value for the plasma clearance of the patient taking phenytoin was more than six standard deviations from the mean for the ten control patients.

Less than 2% of the injected dose of rocuronium was recovered in the urine of this patient over 24 h (range in control patients 0-5%). The patient lost less than 100 ml of blood during the surgery and received no drugs that were not administered to several if not all of the patients in the control group.

| Table 1. Neuromuscular and Pharmacokinetic Variables Following Rocuronium, 600 μg/kg, in a Patient Receiving Phenytoin Chronically and in a Control Group of Patients Not Taking Phenytoin |
|-----------------|-----------------|-----------------|
| Patient Taking Phenytoin | Control Patients (n = 10) |
| Onset (s) | 36 | 63 ± 17 (43-86) |
| Clinical duration (min) | 11 | 54 ± 22 (22-91) |
| Relaxation time (min) | 20 | 81 ± 34 (32-106)* |
| Cl (ml·kg⁻¹·min⁻¹) | 11.5 | 3.0 ± 1.3 (1.8-6.4) |
| Vss (ml/kg) | 355 | 239 ± 77 (142-407) |
| t½β (min) | 36 | 91 ± 21 (69-136) |

Values are mean ± SD; range in parentheses.

Onset: time from administration of rocuronium until complete ablation of T1; Clinical duration: time from administration of rocuronium until T1 recovers to 90%; Relaxation time: time from administration of rocuronium until T1 recovers to 90%; Cl: total plasma clearance; Vss: volume of distribution at steady state; t½β: elimination half-life.

n = 4.

Discussion

In this patient, the duration of action of rocuronium appears to have been decreased by the chronic administration of phenytoin. This interaction is not unique to rocuronium and also has been reported for pancuronium, metocurine, vecuronium, pipercuronium, and doxacurium. This interaction also is not specific to the particular chemical structure of the muscle relaxants, as it has been observed with the steroidal compounds, the bis-benzyloquinolinium, doxacurium, and metocurine, a toxiferene.

This effect of phenytoin to cause resistance to the effects of neuromuscular blocking drugs is a feature of chronic administration, occurring only after at least 1 week of phenytoin administration. In contrast, acute administration of phenytoin results in a potentiation of nondepolarizing neuromuscular block.

The effect of chronic phenytoin administration on the action of neuromuscular blocking drugs has not been demonstrated clearly for d-tubocurarine or atracurium. In a study of the interaction of d-tubocurarine and phenytoin, there was a trend toward decreased duration of action with chronic phenytoin administration, but the sample size was too small to achieve statistical significance. The duration of action of atracurium is unaffected by chronic phenytoin therapy, and atracurium had a normal duration of action in a patient who was resistant to pancuronium. Why phenytoin should fail to influence the duration of atracurium-induced block is unclear, given that carbamazepine, an-


Anesthesiology, Vol 80, No 5, May 1994
other anticonvulsant with neuromuscular effects similar to those of phenytoin, significantly decreases atracurium's duration of action.

The precise mechanisms underlying the interaction of phenytoin and nondepolarizing neuromuscular blocking drugs are not understood fully and may include increased hepatic clearance via induction of specific enzymes in the cytochrome P450 system, decreased protein binding, chronic partial neuromuscular block with denervation-induced proliferation of acetylcholine receptors and the development of a resistance to decreased synthesis and activity of the enzyme acetylcholinesterase. From this report, the only one of these potential mechanisms about which we can speculate is increased hepatic clearance.

Although it is not known whether the P450 system is involved in rocuronium metabolism, in this patient, phenytoin appears to have enhanced the clearance mechanisms of rocuronium. The liver is the principal organ of elimination for rocuronium. In cats, 6 h after a dose of rocuronium, 76% of the drug is found in the liver and bile. In contrast, Ornstein et al. found that the clearance of metocurine was not increased by chronic phenytoin administration. This apparent contradiction may be explained by the fact that metocurine, unlike rocuronium, relies principally on the kidney and not the liver for its elimination. It therefore is not surprising that phenytoin, a drug that affects hepatic enzyme function, does not alter metocurine clearance. The increased clearance of rocuronium was not caused by renal mechanisms, because less than 2% of the drug was recovered in the urine over 24 h; therefore, the increased clearance most likely was due to enhanced hepatic elimination of the drug.

Estimates for clearance can be increased misleadingly by an inadequate sampling time. We obtained blood samples for 360 min in the patient taking phenytoin, but after 180 min, the concentration of vecuronium decreased below detectable levels. Figure 1 shows that within 180 min the bulk of the area under the plasma concentration versus time curve for the patient taking phenytoin was defined clearly. Therefore, the estimate of clearance, which is based on the area under the curve, would not be significantly decreased had we had a more sensitive assay and been able to measure rocuronium concentrations for longer than 180 min.

In summary, we report the case of a patient in whom the duration of action of the new nondepolarizing muscle relaxant rocuronium appeared to be decreased by the chronic administration of phenytoin. We suggest that increased hepatic clearance of the drug is a likely mechanism for this effect.

References

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Anesthesiology, V 80, No 5, May 1994

Fig. 1. Plasma concentration (Cp) versus time curve for a patient taking phenytoin chronically (thick line at bottom) and for a group of patients not receiving the drug (thin lines). The boldface dashed line represents the “average” plasma concentration (determined using a smoother, supersmooth; Modern Regression Methods, S-plus User’s Manual, Version 3.0, Seattle, Statistical Sciences, 1991, pp 1–46). In the patient taking phenytoin, plasma concentrations of rocuronium decreased to less than the lower limit of detection after 180 min. The time at which the kidney is revascularized is indicated by a change from a solid to a dotted line. (Adapted with permission.)
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