Volume 71, No. 2
August 1989

THE JOURNAL OF Anesthesiology
THE AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC.

CLINICAL INVESTIGATIONS

Anesthesiology
71:175–177, 1989

The Effect of H_2-Receptor Antagonist Premedication on the Duration of Vecuronium-Induced Neuromuscular Blockade in Postpartum Patients

Joy L. Hawkins, M.D., Jayshree Adenwala, M.D.,* Cathlyne Camp, M.D.,† Thomas H. Joyce, III, M.D.‡*

The clinical duration of vecuronium was measured in two groups of postpartum patients undergoing elective tubal ligation. Ten patients received no premedication and ten others ranitidine 150 mg orally the morning of surgery. The mean duration of action of vecuronium was 57.2 ± 9.9 min in the unmedicated patients and 54.0 ± 12.9 min in the ranitidine treated patients. These values were significantly greater than the mean value for nonpregnant control patients (35.3 ± 8.4 min) but indistinguishable from the mean value for cimetidine pretreated patients (63.0 ± 17.6 min) reported previously. The combined results of the previous and present studies provide convincing evidence that the clinical duration of vecuronium-induced neuromuscular blockade is significantly longer in the postpartum patient and independent of cimetidine or ranitidine pretreatment. (Key words: Anesthesia: obstetric. Histamine: cimetidine; ranitidine. Neuromuscular relaxants: vecuronium.)

VECURONIUM'S INTERMEDIATE DURATION of action makes it useful for short surgical procedures. Although these could include cases of postpartum tubal ligation, we have reported a prolonged duration of action of vecuronium in the postpartum period.[1] Postpartum patients receive as preanesthetic medications histamine-2 (H_2) receptor antagonist drugs such as cimetidine or ranitidine to reduce gastric acid secretion. These drugs, notably cimetidine, have been reported to increase the duration of action of some drugs dependent upon hepatic elimination.[2] In our previous study, the postpartum patients received preoperative cimetidine while the nonpregnant control patients did not. It was, therefore, not possible to determine whether the prolonged action of vecuronium in the postpartum patients was due to cimetidine pretreatment or to the postpartum status.

The present studies, an extension of the earlier investigation, measured the duration of vecuronium-induced neuromuscular blockade in unmedicated postpartum patients and in postpartum patients pretreated with ranitidine, a histamine-2 (H_2) receptor antagonist that has little effect on hepatic metabolism of other drugs.[2]

Materials and Methods

This study was undertaken with Institutional Review Board approval and informed patient consent. The clinical duration of vecuronium was studied in two groups of ten postpartum patients each, scheduled for elective tubal ligation. One group received no preanesthetic medication and the other ranitidine 150 mg orally the morning of surgery. No patient was receiving magnesium sulfate, antibiotics, or any drugs other than vitamins and analgesics.

* Assistant Professor of Anesthesiology, Baylor College of Medicine, Houston, Texas.

† Attending in Anesthesiology, St. Joseph's Hospital, Houston, Texas.

‡ Professor and Acting Chairman of Anesthesiology, Baylor College of Medicine, Houston, Texas.

Received from the Department of Anesthesiology, Baylor College of Medicine, Houston, Texas. Accepted for publication February 28, 1989. Supported by a grant from Organon, Inc., West Orange, New Jersey. Presented at the 1987 Annual Meeting of the American Society of Anesthesiologists in Atlanta.

Address reprint requests to Dr. Hawkins: Department of Anesthesiology, Baylor College of Medicine, One Baylor Plaza, Houston, Texas 77030.

TABLE 1. Clinical Duration of Vecuronium Blockade (Mean ± SD) in Nonpregnant Control and Postpartum Patients

Group	Nonpregnant	Postpartum		
Pretreatment	None (10)†	None (10)	Cimetidine (10)†	Ranitidine (10)
Duration (min)	35.3 ± 8.4	57.2 ± 9.9*	63.0 ± 17.6*	54.0 ± 12.9*

(10) = Number of patients studied.
* $P < 0.01$ with respect to nonpregnant controls.
† Data from previous report from this institution.[1]

All patients received 10 mg metoclopramide iv and 30 ml sodium citrate orally in the preoperative holding area.

In the operating room, neuromuscular blockade was monitored with a peripheral nerve stimulator (NeuroStim II®, Neuro Technology Inc., Houston, TX) using surface electrodes over the ulnar nerve at the wrist. Following the induction of anesthesia with fentanyl, 2 μg/kg, and thiopental, 3 mg/kg iv, a baseline train-of-four twitch response was observed. Vecuronium 0.1 mg/kg was then given iv with a complete loss of twitch response in each patient. Tracheal intubation was performed and anesthesia maintained using 70% nitrous oxide and 30% oxygen with supplemental intravenous fentanyl and thiopental at the discretion of the anesthesiologist managing the patient. The train-of-four twitch response was monitored every 12 s throughout the duration of the procedure by an independent observer unaware of the group to which the patients belonged. The clinical duration of vecuronium was defined as the time from administration to the return of the fourth twitch in the train-of-four sequence.

The data were analyzed statistically using planned comparisons analysis of variance and a $P < .01$ was considered significant. Variability is expressed as the standard deviation.

Results

The mean duration of action of vecuronium in the unmedicated postpartum patients was 57.2 ± 9.9 min and 54.0 ± 12.9 min in the ranitidine-treated patients. As illustrated in table 1, these values were significantly greater than the mean value for the nonpregnant control patients but not different from the mean value for the cimetidine pretreated patients in the previous study.[1]

Discussion

Vecuronium bromide is a muscle relaxant which is characterized as having an intermediate duration of action. Following an intravenous dose of 0.1 mg/kg, clinical duration has been reported to be between 25 and 40 min in nonpregnant patients receiving a variety of premedicant drugs and anesthetics, and undergoing a wide range of surgical procedures.[3,4]

In contrast to these findings, a previous report by us determined that the clinical duration of vecuronium was significantly prolonged in postpartum patients pretreated with cimetidine and undergoing elective tubal ligation (table 1).[1] The present studies provide new information that the duration of action of vecuronium is also prolonged in unpremedicated and ranitidine pretreated postpartum patients. The combined results of the previous and present studies provide convincing evidence that the clinical duration of vecuronium-induced neuromuscular blockade is significantly longer in the postpartum patient and independent of pretreatment with either cimetidine or ranitidine.

Vecuronium is rapidly cleared from plasma by hepatic uptake. The disposition of an intravenous dose of vecuronium has been found to be about 20–25% excreted in urine, 40% excreted in bile, and 15% bound in the liver.[5] Only 10% is present in the urine as the 3-hydroxy metabolite, while the 17-hydroxy and 3,17-hydroxy metabolites are undetectable.[6,7] Although the 3-OH metabolite is only slightly less potent than the parent compound as a neuromuscular blocking agent, its concentrations in plasma are undetectable, and it is therefore unlikely to contribute to the pharmacologic effect. The 17-OH and 3,17-OH metabolites have very low neuromuscular activity.[8]

The H_2 receptor antagonist drug cimetidine decreases clearance of drugs having a high hepatic extraction such as lidocaine and propranolol. This effect is due primarily to inhibition of hepatic microsomal mixed-function oxidases such as cytochrome P-450 rather than a decrease in hepatic blood flow. Ranitidine has a very low affinity for hepatic cytochrome P-450, and drug interactions leading to altered clearance have not been shown to occur with this H_2 receptor antagonist.[2] Vecuronium's rapid clearance and short elimination half-life are mainly due to rapid hepatic uptake and biliary excretion rather than metabolism, and therefore would not be affected by alterations in enzyme function. The postpartum patients in these studies received only one dose of the H_2 receptor antagonist drug the morning of surgery. The patients did not receive chronic treatment, a regimen more likely to cause inhibition of hepatic microsomal enzyme activity.

Compared to the nonpregnant control group in our first study,[1] the clinical duration of vecuronium in postpartum patients was prolonged by over 50%. There are no studies of vecuronium pharmacokinetics in postpartum patients; however, Dailey *et al.* found that the elimination

half-life for vecuronium was shorter in patients undergoing cesarean section than in nonpregnant patients undergoing surgery.[9] In addition, total clearance was higher in patients undergoing cesarean section. They speculated that acute volume shifts at delivery, removal of the fetus and placenta with any drug contained in these tissues, or stimulation of hepatic microsomal enzymes by progesterone could be causes of the increased clearance of vecuronium. In contrast, Rodrigue *et al.* reported that, in pregnant rabbits, the ED50 of vecuronium was less than half that of nonpregnant animals, and that recovery times in pregnant animals were significantly prolonged.[10]

In examining the duration of succinylcholine in postpartum patients, Leighton *et al.*[11] found no difference in time to recovery between term pregnant and nonpregnant patients, but a significantly increased duration of action in postpartum patients. They concluded that the difference between term pregnant and postpartum patients with respect to neuromuscular blockade might have been a decrease in the volume of distribution postpartum resulting in a greater effective concentration of succinylcholine at the neuromuscular junction. Ueland[12] measured blood volume changes at delivery and found a decrease of 16.2% in the first 3 days postpartum from a term pregnant value of 6 l (83.3 ml/kg). However, it required 6 weeks postpartum to return to a blood volume of 4 l (71.2 ml/kg).

Thus, although postpartum patients have a smaller blood volume than term pregnant patients during the first 48 h postpartum when tubal ligations are usually performed, their blood volume is still larger than that in nonpregnant patients. Vecuronium also has a longer duration of action in infants than in adults, which is similarly attributed to their larger volume of distribution.[13] That is, more vecuronium is in the peripheral compartment and not available for excretion by the organs of elimination.

Another possible explanation for the prolonged duration of vecuronium action in postpartum patients is the use of the higher postpartum weight as opposed to the prepregnant or ideal body weight for calculating the relaxant dose. The vecuronium dose of 0.1 mg/kg used in this study was based on the patient's weight the morning of surgery. Generally, this weight represented an increase over prepregnant or ideal body weight. It has been shown that duration of action of vecuronium increases linearly with the dose.[1,14,15] Therefore, it is possible that if the vecuronium dose had been adjusted by using ideal body weight, the clinical duration of neuromuscular blockade might have been reduced.

In conclusion, a significantly longer clinical duration of vecuronium-induced neuromuscular blockade was found in postpartum patients compared with that in nonpregnant controls. The duration of action was unaffected by premedication with ranitidine and was similar to that in postpartum patients pretreated with cimetidine.[1] It is postulated that this clinically significant increase in neuromuscular blockade may be due to alterations in blood volume, or the volume of distribution that occurs in the postpartum period. The prolonged action of vecuronium in the postpartum patients may be clinically important when using the drug in short surgical procedures such as tubal ligation, and suggests that the dosage of vecuronium should be reduced in the postpartum period, and the level of neuromuscular blockade monitored closely.

References

1. Camp CE, Tessem J, Adenwala J, Joyce TH III: Vecuronium and prolonged neuromuscular blockade in postpartum patients. ANESTHESIOLOGY 67:1006–1008, 1987
2. Jackson JE, Bentley JB, Glass SJ, Fukui T, Gandolfi AJ, Plachetka JR: Effects of histamine-2 receptor blockade on lidocaine kinetics. Clin Pharmacol Ther 37:544–548, 1985
3. Torda TA: The new relaxants. A review of the clinical pharmacology of atracurium and vecuronium. Anaesth Intensive Care 15:72–82, 1987
4. Agoston S: Clinical pharmacology of vecuronium: A preliminary report on a multicentre study in 800 patients, Clinical Experiences with Norcuron (Org NC 45, vecuronium bromide). Edited by Agoston S, Bowman WC, Miller RD, Viby-Mogensen J. Geneva, Exerpta Medica, 1983, pp 99–108
5. Bencini AF, Scaf AHJ, Agoston S, Houwertjes MC, Kersten UW: Disposition of vecuronium bromide in the cat. Br J Anaesth 57: 782–788, 1985
6. Bencini A, Scaf AHJ, Sohn YJ, Meistelman C, Lienhart A, Kersten UW, Schwarz S, Agoston S: Disposition and urinary excretion of vecuronium bromide in anesthetized patients with normal renal function or renal failure. Anesth Analg 65:245–251, 1986
7. Booij LHDJ, Vree TB, Hurkmans F, Reekers-Ketting JJ, Crul JF: Pharmacokinetics and pharmacodynamics of the muscle relaxant drug Org NC-45 and each of its hydroxy metabolites in dogs. Anaesthesist 30:329–333, 1981
8. Marshall IG, Gibb AJ, Durant NN: Neuromuscular and vagal blocking actions of pancuronium bromide, its metabolites, and vecuronium bromide (Org NC-45) and its potential metabolites in the anaesthetized cat. Br J Anaesth 55:703–713, 1983
9. Dailey PA, Fisher DM, Shnider SM, Baysinger CL, Shinohara Y, Miller RD, Abboud TK, Kim KC: Pharmacokinetics, placental transfer, and neonatal effects of vecuronium and pancuronium administered during cesarean section. ANESTHESIOLOGY 60: 569–574, 1984
10. Rodrigue R, Durant NN, Nguyen BS, Katz L, Conklin KA: Comparison of vecuronium-induced neuromuscular blockade in pregnant and nonpregnant female rabbits (abstract). ANESTHESIOLOGY 65:A401, 1986
11. Leighton BL, Cheek TG, Gross JB, Apfelbaum JL, Shantz BB, Gutsche BB, Rosenberg H: Succinylcholine pharmacodynamics in peripartum patients. ANESTHESIOLOGY 64:202–205, 1986
12. Ueland K: Maternal cardiovascular dynamics VII. Intrapartum blood volume changes. Am J Obstet Gynecol 126:671–677, 1976
13. Fisher DM, Castagnoli K, Miller RD: Vecuronium kinetics and dynamics in anesthetized infants and children. Clin Pharmacol Ther 37:402–406, 1985
14. Feldman SA, Liban JB: Vecuronium—A variable dose technique. Anaesthesia 42:199–201, 1987
15. Ginsberg B, Glass PSA, Shafron BS, Mace J, Quill T, Mardekian J: Onset, duration and recovery following high dose vecuronium (abstract). ANESTHESIOLOGY 67:A341, 1987