Clinical Report

Increased cis-atracurium requirements during prolonged administration to a child

Joseph D Tobias MD

Purpose: To report increased infusion requirements of cis-atracurium during prolonged infusion (six weeks) to provide neuromuscular blockade in a child during prolonged mechanical ventilation. Despite a previous study in adult patients which demonstrated no increase in infusion requirements over five days, we noted a considerable increase over six weeks.

Clinical features: A seven month old infant required prolonged mechanical ventilation and neuromuscular blockade following an episode of multi-system organ failure from pseudomembranous colitis. The infusion of cis-atracurium was adjusted according to the train-of-four response obtained with a peripheral nerve stimulator using standard train-of-four monitoring. Initial infusion requirements which were 2.8 $\mu g \cdot kg^{-1}$ min^{-1} on day # 1 increased to 22.3 $\mu g \cdot kg^{-1}$ min^{-1} on day #40.

Conclusion: Increased infusion requirements were necessary during the prolonged administration of cis-atracurium to a critically ill infant. Titration of the dose based on monitoring with a peripheral nerve stimulator is recommended.

Objectif : Rapporter l'augmentation des besoins de cis-atracurium pendant une perfusion de longue durée (six semaines) utilisée pour curariser un enfant pendant la ventilation mécanique. Malgré une étude antérieure qui démontrait chez les adultes une augmentation importante des besoins survenant en cinq jours, ici, l'importante augmentation a été constatée en six semaines.

Éléments cliniques : Un enfant de sept mois a eu besoin de ventilation mécanique prolongée avec curarisation à la suite d'une défaillance multiviscérale causée par une colite pseudomembraneuse. La perfusion de cis-atracurium était réglée selon la réponse au train-de-quatre monitorée avec un stimulateur nerveux périphérique. Les besoins initiaux de la perfusion qui étaient de 2,8 $\mu g \cdot kg^{-1}$ min^{-1} sont passés à 22 $\mu g \cdot kg^{-1}$ min^{-1} à la quarantième journée.

Conclusion : Il a été nécessaire d'augmenter une perfusion de cis-atracurium de longue durée chez un enfant gravement malade. Il est recommandé d'ajuster la dose de curare avec un moniteur périphérique pour le bloc neuromusculaire.

From the Departments of Child Health and Anesthesiology, the Division of Pediatric Critical Care/Anesthesia, the University of Missouri, Columbia, Missouri.

Address correspondence to: Dr. Joseph D Tobias, Pediatric Critical Care/Anesthesia, The University of Missouri, Department of Child Health, M658 Health Sciences Center, One Hospital Drive, Columbia, MO 65212, USA. TEL: 573 882-6544; FAX: 573 882-2742;

Accepted for publication September 20, 1996.

SEVERAL situations may arise which necessitate the use of neuromuscular blocking agents in children in the Paediatric Intensive Care Unit (PICU).[1] While there remain several appropriate choices for providing neuromuscular blockade in children;[1] in the ICU setting when patients develop hepatic or renal failure, the clearance of many of these agents may be altered. The duration of effect of vecuronium, pancuronium, and rocuronium may be altered in the setting of renal and/or hepatic dysfunction.[1,2]

Since the effect of atracurium is not altered in patients with end-organ dysfunction, it may be a more appropriate choice in the ICU. Atracurium is degraded by non-specific ester hydrolysis and Hofman degradation and therefore its effect is not altered by hepatic or renal failure. Possible problems with the bolus administration of atracurium include histamine release leading to bronchospasm and/or hypotension. Cis-atracurium is a new, intermediate benzylisoquinolinium neuromuscular blocking agent. It is one of 10 stereoisomers of atracurium and it may be appropriate in the ICU patient because of its non-organ dependent elimination, minimal propensity to release histamine, and lack of autonomic effects.[3,4]

We are unaware of previous reports concerning the use of cis-atracurium for prolonged neuromuscular blockade in a child. Additionally, the company-provided information concerning cis-atracurium (Glaxo Wellcome Inc, Research Triangle Park, North Carolina) states that "the mean infusion requirement required to maintain adequate relaxation remained relatively stable for up to five days (during clinical trials)."[4] We present information concerning infusion requirements of cis-atracurium during prolonged infusion (40 days) in a seven month old with multi-system organ failure.

Case report

A seven month old, 10.4 kg infant was admitted for dehydration and profuse diarrhoea. The past medical history was positive for Hirschsprung's disease which had been treated by colostomy during infancy followed by a rectal pull through procedure. Prior to admission the infant had been treated with amoxicillin for otitis media. Following admission, the infant developed progressive abdominal distention and ongoing diarrhoea that required large amounts of fluid to maintain intravascular volume. The stool was positive for *C. difficile* toxin. Increased abdominal distention led to respiratory compromise necessitating tracheal intubation and mechanical ventilation. A large amount of ascites (550 ml) developed that was drained with a peritoneal catheter. Because of progressive respiratory compromise from the abdominal distention and the inability to ventilate and oxygenate adequately, the patient was taken to the operating room for an exploratory laparotomy. A total colectomy was performed and the abdomen was closed with a synthetic patch since the bowel was edematous thus preventing primary closure. Postoperatively, fentanyl and midazolam infusions were started for sedation/analgesia and a cis-atracurium infusion for neuromuscular blockade. The cis-atracurium was administered as a bolus dose of 0.1 $mg \cdot kg^{-1}$ followed by an infusion of 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Neuromuscular blockade was monitored according to our usual protocol in our Pediatric ICU. This incudes use of a peripheral nerve stimulator (Peripheral Nerve Stimulator NS252, Fisher & Paykel, Auckland, New Zealand) applied to either the ulnar or peroneal nerve. Train-of-four (TOF) stimulation was at 50 mA at 2 Hz for two seconds. The TOF was monitored every two to four hours and the infusion adjusted to maintain one twitch of the TOF. When two or more twitches were apparent, a bolus dose was administered (equivalent to the current hourly rate) and the infusion rate was increased by 15 to 20%.

The postoperative course was prolonged and complicated by hepatic dysfunction with elevated liver enzymes and bilirubin, renal insufficiency, disseminated intravascular coagulation, non-cardiogenic pulmonary oedema. The cis-atracurium infusion requirements during the six week hospital course are listed in the table. The patient eventually died from multi-system organ failure.

TABLE Cis-atracurium infusion requirements*

Day	$\mu g \cdot kg^{-1}\ min^{-1}$
1	2.8
5	3.0
10	4.4
15	6.1
20	7.2
25	10.2
30	16.7
35	19.4
40	22.3

*The infusion requirement represents the mean cis-atracurium infusion rate for each 24 hour period.

Discussion

Because of its lack of cardiovascular effects and its non-organ dependent elimination, cis-atracurium may be a suitable agent for neuromuscular blockade in the Paediatric ICU patient especially those with renal or hepatic dysfunction. There are no previous reports

concerning its use for providing prolonged neuromuscular blockade in children. Prielipp *et al.* compared cis-atracurium with vecuronium for neuromuscular blockade in adult patients.[4] Patients received the drug for 24 to 145 hr (mean 80±7 hr). They noted cis-atracurium infusion requirements varying from 0.9 to 6.9 $\mu g \cdot kg^{-1}\ min^{-1}$ with a mean infusion rate of 2.6±0.2 $\mu g \cdot kg^{-1}\ min^{-1}$. In 11 patients that received cis-atracurium for at least five days, two had a reduction in the infusion rate, one had no change, while eight required an increase in the mean infusion rate.

We noted an increase in the infusion requirements in our patient over six weeks. Similar increases have been noted with other neuromuscular blocking agents[5–7] and practitioners should also expect a similar increase with the newer agent, cis-atracurium. Kushimo *et al.*[7] noted increased dosing requirements of atracurium within 72 hr of starting an infusion. In our previous studies with rocuronium[5] and pancuronium,[6] although increases were noted from day to day, it was not until day five that the increase reached statistical significance.

Several factors may affect dosing requirements of neuromuscular blocking agents in the Paediatric ICU patient including concurrently administered medications, alterations in cardiovascular function, and changes in renal/hepatic function. Based on the variability of infusion requirements of any neuromuscular blocking agent in the Paediatric ICU patient, monitoring of neuromuscular transmission with a peripheral nerve stimulator is mandatory. One cause of the increased infusion requirements over time is upregulation of acetylcholine receptors at the neuromuscular junction.[8,9] Dodson *et al.*[8] have demonstrated an increased density of acetylcholine receptors in muscle from patients who have received prolonged infusions of neuromuscular blocking agents suggesting that prolonged neuromuscular blockade, like partial or complete deafferentation injury, leads to proliferation of acetylcholine receptors.

Several agents have been shown to provide acceptable neuromuscular blockade in the paediatric ICU patient. Cis-atracurium offers the advantages of limited cardiovascular effects and non-organ dependent elimination. Like other neuromuscular blocking agents, increased dose requirements are to be expected with prolonged administration. Based on the many variables that may affect infusion requirements of neuromuscular blocking agents in the Paediatric ICU setting, titration of the dose based on monitoring with a peripheral nerve stimulator is recommended.

References

1 *Sharpe MD.* The use of muscle relaxants in the intensive care unit. Can J Anaesth 1992; 39: 949–62.

2 *Magorian T, Wood P, Caldwell J, et al.* The pharmacokinetics and neuromuscular effects of rocuronium bromide in patients with liver disease. Anesth Analg 1995; 80: 754–9.

3 *Bluestein LS, Stinson LW Jr, Lennon RL, Quessy SN, Wilson RM.* Evaluation of cisatracurium, a new neuromuscular blocking agent, for tracheal intubation. Can J Anaesth 1996; 43: 925–31.

4 *Prielipp RC, Coursin DB, Scuderi PE, et al.* Comparison of the infusion requirements and recovery profiles of vecuronium and cisatracurium 51W89 in intensive care unit patients. Anesth Analg 1995; 81: 3–12.

5 *Tobias JD.* Continuous infusion of rocuronium in a paediatric intensive care unit. Can J Anaesth 1996; 43: 353–7.

6 *Tobias JD, Lynch A, McDuffee A, Garrett JS.* Pancuronium infusion for neuromuscular block in children in the Pediatric Intensive Care Unit. Anesth Analg 1995; 81: 13–6.

7 *Kushimo TO, Darowski MJ, Morris P, Hollis S, Meakin G.* Dose requirements of atracurium in paediatric intensive care patients. Br J Anaesth 1991; 67: 781–3.

8 *Dodson BA, Kelly BJ, Braswell LM, Cohen NH.* Changes in acetylcholine receptor number in muscle from critically ill patients receiving muscle relaxants: an investigation of the molecular mechanism of prolonged paralysis. Crit Care Med 1995; 23: 815–21.

9 *Martyn JAJ, White DA, Gronert GA, Jaffe RS, Ward JM.* Up-and-down regulation of skeletal muscle acetylcholine receptors. Effects on neuromuscular blockers. Anesthesiology 1992; 76: 822–43.