CASE REPORT

**Accidental Epidural Injection of Rocuronium in a Pediatric Patient:
A Case Report and Literature Review**

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Accidental administration of non-epidural drugs into the epidural or subarachnoid spaces may be associated with unexpected pain, morbidity, adverse effects, increased level of care, prolonged hospital stay, and mortality. We describe a 12-month-old admitted for secondary-stage hypospadias reconstruction. General anesthesia was induced with sevoflurane and a peripheral catheter was placed. Instead of ropivacaine, rocuronium (80 mg; 6.3 mg/kg) was injected into the epidural space by the caudal route. Surgery was uneventful and was completed 160 minutes after rocuronium was given. The patient exhibited paralysis with 1 of 4 twitches to the train-of-four with some posttetanic potentiation at the end of surgery. He was transferred to the pediatric intensive care unit for supportive ventilation and recovery. He did not experience oxygen desaturation or hypoventilation between the time of rocuronium administration and intubation. He was hemodynamically stable, without respiratory insufficiency, and his neurologic exam was normal, without motor or sensorial block. The patient was discharged home on the morning of the first postoperative day. Clinical examination 1 week after surgery revealed no lasting sequelae from the error.

INDEX TERMS: epidural, intrathecal, intraventricular, medication error, neuromuscular blocker, rocuronium

J Pediatr Pharmacol Ther 2016;21(5):436–443

INTRODUCTION

Epidural and subarachnoid analgesia are commonly used to block pain transmission for surgical procedures. Accidental administration of non-epidural drugs into the epidural or subarachnoid spaces may be associated with unexpected pain, morbidity, adverse effects, increased level of care, prolonged hospital stay, and mortality. The present case report describes a pediatric patient who experienced systemic neuromuscular blockade from accidental epidural injection of rocuronium instead of ropivacaine prior to an elective surgery. A summary of the literature will also be provided regarding other cases in which non-depolarizing neuromuscular blockers were accidentally administered into the central nervous system.

CASE REPORT

A 12-month-old, 12.7-kg, American Society of Anesthesiologists physical status I male was admitted for secondary-stage hypospadias reconstruction (urethroplasty and cystoscopy) us-

ing general endotracheal anesthesia and caudal regional anesthesia. The patient's past medical history was significant for primary-stage hypospadias/chordee repair with scrotoplasty and cystoscopy 9 months prior. In the operating room, the patient was placed in the supine position. General anesthesia was induced with sevoflurane via facemask. After loss of consciousness, a peripheral intravenous catheter and laryngeal mask airway were easily placed and sevoflurane was continued. Cefazolin was administered for perioperative surgical wound prophylaxis. Lactated Ringer's solution was infused via peripheral catheter. Ropivacaine 0.2% was then intended to be injected into the epidural space using the caudal approach. However, rocuronium was selected instead of ropivacaine. Eighty milligrams (6.3 mg/kg) of rocuronium (10 mg/mL) was subsequently administered to the patient by the caudal route. Thirteen minutes passed before the error was discovered and the anesthesiologist was alerted that ropivacaine had not been opened and that a partial vial of rocuronium was in the surgical suite. After consultation with the

Table 1. Vital Signs and Oxygenation

	Pre-Op Value	Value at Hourly Increments											
		2	4	6	8	10	12	14	16	18	20	22	23
Temperature (°C)	37.1	37	36	36	37	36.6	NA	36.9	NA	36.9	36.6	NA	Discharged
HR (beats/min)	125	135	124	113	116	98	150	135	155	130	140	154	
RR (breaths/min)	28	20	20	19	19	19	28	28	27	28	28	30	
SBP (mm Hg)	103	80	91	83	91	77	94	NA	NA	NA	NA	NA	
DBP (mm Hg)	40	50	42	35	41	35	59	NA	NA	NA	NA	NA	
MAP (mm Hg)	NA	NA	NA	55	56	49	65	NA	NA	NA	NA	NA	
FiO ₂ (%)	21	30	30	30	30	30	RA	RA	RA	RA	RA	RA	
O ₂ Saturation (%)	99	99	99	99	99	100	97	97	96	98	95	97	
Airway type	None	V	V	V	V	V	V	U	U	U	U	U	

DBP, diastolic blood pressure; FiO₂, fraction inspired oxygen; HR, heart rate; MAP, mean arterial pressure; NA, not available; RA, room air; RR, respiratory rate; SBP, systolic blood pressure; U, unassisted airway; V, ventilator

patient's parents, it was decided to continue with the operation. The surgery itself was uneventful and was completed 160 minutes after the single erroneous dose of caudal rocuronium. The patient exhibited 1 of 4 twitches to the train-of-four with some posttetanic potentiation at the end of surgery. He did not generate any spontaneous breaths. At that point, the patient was sedated with midazolam and fentanyl, was intubated, and was started on a propofol drip for transfer to the pediatric intensive care unit for monitoring and supportive care.

Thirteen hours after the epidural injection, the patient was extubated. He was restless following extubation, but he eventually fell asleep for the night. He was hemodynamically stable without respiratory insufficiency. His neurologic exam was normal and without motor or sensorial block. Morphine and oxycodone were administered for surgical pain. The patient was discharged home on the morning of the first postoperative day.

The patient did not experience oxygen desaturation or hypoventilation between the time of rocuronium administration and intubation. The patient's blood pressure and respiratory parameters and electrocardiogram waveform remained consistent and within normal limits from the patient's preoperative baseline until hospital discharge (Table 1). However, the patient's heart rate increased mildly from a baseline rate of 125 beats/min to 137 to 150 beats/min in the 45 minutes after the rocuronium injection. The heart rate then lowered to 125 to 135 beats/min for the remainder of the surgery. The heart rate gradu-

ally lowered until 12 hours after surgery, when the patient was extubated. Clinical examination 1 week after surgery revealed no lasting sequelae from the error.

LITERATURE REVIEW

Medline and Embase were searched to find publications containing the search terms "vecuronium," "pancuronium," "rocuronium," "atracurium," "cisatracurium," or "mivacurium" and "intrathecal," "intraventricular," or "epidural." Twelve case reports were identified (Table 2). Two out of the 12 cases were reported in Japanese but included an abstract written in English.^{1,2} Accidental epidural injection of neuromuscular blockers included atracurium (2 cases), cisatracurium (1 case), pancuronium (2 cases), rocuronium (3 cases, 1 with morphine and 1 with etomidate), and vecuronium (4 cases). All cases occurred in adults ranging in age range from 22 to 67 years. Neuromuscular blockade was reversed in 7 patients with neostigmine and atropine.²⁻⁸ One patient was given pyridostigmine and glycopyrrolate at the end of surgery for reversal.⁹ In each of these 8 cases, an acetylcholinesterase inhibitor plus an anticholinergic drug resulted in improvement and recovery of the patient's clinical condition without lasting sequelae. In one case, the patient was administered epidural dexamethasone in normal saline as a treatment.¹⁰ No reversal drugs were administered in the remaining 3 cases. Two of these patients improved spontaneously with supportive care (intubation, analgesics, oxygen).^{1,11} One patient

Table 2. Published Case Reports of Non-Depolarizing Neuromuscular Blockers Administered into the Central Nervous System

Reference	Age, Weight, Sex	Surgery	Drug(s) Given (Route)	Drug(s) Intended	Sequelae, Intervention and Outcome
Peduto et al ³	35 yr, 65 kg, F	C-section	Pancuronium (Subarachnoid)	Bupivacaine	<i>Sequelae:</i> Progressive and generalized muscle hypotonia; inability to breathe adequately; slightly cyanotic and agitated <i>Intervention:</i> Oxygen; neostigmine and atropine <i>Outcome:</i> Normal muscle movement and sensation after 1 hr; no change in neurological examination on postoperative day 2; no sequelae 3 mo after error
Kasaba et al ¹	NA	NA	Vecuronium (Epidural)	NA	<i>Sequelae:</i> None <i>Interventions:</i> None <i>Outcome:</i> No neurological complications
Kostopanagiotou et al ⁴	40 yr, 65 kg, F	Hemorrhoidectomy	Vecuronium (Epidural)	Ropivacaine	<i>Sequelae:</i> Recovery of TOF response was 10%, 25%, 50%, and 50% at 80, 90, 100, and 105 min, respectively <i>Interventions:</i> Epidural NaCl 0.9%; IV neostigmine and IV atropine when TOF reached 70% <i>Outcome:</i> Fully awake, oriented, and able to follow commands after 5 min; no signs of sensor or motor blockade 2 hr after error; discharge 6 hr after error; no neurotoxicity 2 mo after error
Salihoglu et al ¹¹	22 yr, 70 kg, F	Hemorrhoidectomy	Atracurium (Subarachnoid)	Bupivacaine	<i>Sequelae:</i> Diplopia, blurred vision, general discomfort, hypotension, and tachycardia during administration; discomfort, hypotension, and tachycardia resolved after 2 min; muscle hypotonia occurred after 5 min (TOF was 50% at the adductor pollicis) <i>Interventions:</i> Oxygen <i>Outcome:</i> Normal sensory and motor function 1 hr after error; normal neurological examination at 1 wk and 1 mo
Vassilakos et al ¹⁰	65 yr, 70 kg, F	Intestinal resection for colon cancer	Cisatracurium (Epidural)	Bupivacaine	<i>Sequelae:</i> NA <i>Interventions:</i> Dexamethasone 1 mg/mL; 0.9% NaCl epidurally 22 min after error <i>Outcome:</i> Complete recovery. No neurotoxicity 80 min and 2 days after error. No complications 1 and 14 mo later
Kratajian and Laen ¹⁵	41 yr, 51 kg, M	Anteroposterior resection	Pancuronium (Epidural)	Fentanyl	<i>Sequelae:</i> Uneventful 3-hr surgery; patient spontaneously started breathing during skin suturing <i>Interventions:</i> Neostigmine and atropine IV postoperatively <i>Outcome:</i> No signs of neurotoxicity 2 mo after error

TOF, Train of four monitoring

Table 2. Published Case Reports of Non-Depolarizing Neuromuscular Blockers Administered into the Central Nervous System (cont.)

Reference	Age, Weight, Sex	Surgery	Drug(s) Given (Route)	Drug(s) Intended	Sequelae, Intervention and Outcome
Cesur et al ⁶	53 yr, 80 kg, M	Rectal abscess	Rocuronium plus Morphine (Caudal)	Lidocaine plus Morphine	<p><i>Sequelae:</i> Pain and burning during injection; difficulty breathing and speaking 15 sec after injection; surgery completed 45 min after error</p> <p><i>Interventions:</i> Oxygen; neostigmine 2.5 mg and atropine 1 mg IV given postoperatively</p> <p><i>Outcome:</i> Normal neurologic findings except pinpoint pupils after 10 min; pupil size of 2 mm after 1 day, but normal after 30 hr; no signs of neurotoxicity 1 mo after error</p>
Yachiyo and Tabuchi ²	55 yr, 63 kg, M	Cholecystectomy	Vecuronium (Epidural)	Ropivacaine	<p><i>Sequelae:</i> No back pain during injection; surgery was completed 120 min after the error</p> <p><i>Interventions:</i> Neostigmine 2 mg and atropine 1 mg IV given postoperatively</p> <p><i>Outcome:</i> Normal motor function after neostigmine/atropine; extubation after 4 min; no respiratory insufficiency or neurological sequelae</p>
Howell and Driver ¹²	61 yrs, 100 kg, M	Craniotomy for cerebral hemorrhage secondary to an aneurysm	Etomidate plus Rocuronium (Ventriculostomy)	Etomidate plus Rocuronium (IV)	<p><i>Sequelae:</i> Loss of consciousness and apnea</p> <p><i>Interventions:</i> None</p> <p><i>Outcome:</i> Infarctions in the right temporoparietal lobe and bilateral periventricular white matter; persistent vasospasm; postbleed day 30; death</p>
Shin et al ⁹	48 yr, 67 kg, M	Cystectomy	Rocuronium (Epidural)	Lidocaine plus Epinephrine	<p><i>Sequelae:</i> Burning during injection; shortness of breath; TOF was 25% 10 min after injection, 10% after 40 min, 70% after 130 min</p> <p><i>Interventions:</i> Pyridostigmine and glycopyrrolate IV given postoperatively</p> <p><i>Outcome:</i> Normal neurological findings; no motor or sensorial block after 15 min, 1 day, and 2 mo</p>
Furuya et al ⁷	67 yr, 49.3 kg, F	Stoma closure	Vecuronium (Epidural)	Vecuronium (IV)	<p><i>Sequelae:</i> Surgery was performed uneventfully</p> <p><i>Interventions:</i> Neostigmine and atropine IV given postoperatively</p> <p><i>Outcome:</i> No sensory or motor injury</p>
Zirak et al ⁸	38 (62), F	Hysterectomy	Atracurium (Subarachnoid)	Bupivacaine	<p><i>Sequelae:</i> No sensory or motor block, hemodynamically stable, TOF was 60% after 10 min and >90% after 50 min; uneventful surgery</p> <p><i>Intervention:</i> Neostigmine and atropine IV given postoperatively</p> <p><i>Outcome:</i> Normal sensory, motor and reflex maneuver 2 days, 1 wk, 2 wk, and 1 mo after error</p>

TOF, Train of four monitoring

Table 3. Physiochemical Properties of Neuromuscular Blocking Agents and Local Anesthetics^{19,21}

Drug	Atracurium/ Cisatracurium	Rocuronium	Vecuronium	Pancuronium	Lidocaine	Ropivacaine	Bupivacaine
Protein binding (% bound)	47	56	69	21	65	94	95
Molecular weight (g/mol)	929	546	558	573	234	274	288
Lipid solubility	-3.98*	-1.68*	-0.75*	0.003†	1†	2.9†	10†
pH	3.0-3.7	4	3.5-4.5	3.8-4.2	5-7	4.5-5	4-6.5
Excipients	Benzene sulfonic acid; benzyl alcohol	Sodium acetate, sodium chloride, acetic acid, and/or sodium hydroxide	Citric acid anhydrous, dibasic sodium phosphate anhydrous, mannitol, sodium hydroxide and/or phosphoric acid	Sodium acetate, benzyl alcohol, sodium chloride; acetic acid; sodium hydroxide	Sodium chloride, sodium hydroxide, and/ or hydrochloric acid	Sodium chloride, sodium hydroxide, and/ or hydrochloric acid	Sodium chloride, sodium hydroxide, and/ or hydrochloric acid

* Distribution coefficient (Log D) method

† Partition coefficient method

died after receiving supportive care after intracerebroventricular injections of etomidate and rocuronium.¹²

DISCUSSION

No cases have been reported in the literature describing the accidental administration of a neuromuscular blocker into the central nervous system of a pediatric patient. In adults, hemodynamic instability and neurologic toxicity, if present, are not significant features. However, because the case reports occurred during general anesthesia, side effects or other symptoms may have been masked. Nevertheless, administration of neuromuscular blockers into the central nervous system could possibly cause neurological sequelae. For example, one study¹³ of an *in vitro* hippocampal cell culture demonstrated that a pH of 6.6 induced neuronal losses from necrosis and apoptosis. Rocuronium is prepared in aqueous solution and adjusted to a pH of 4.¹⁴ At this pH, it could be damaging to central nervous system tissues if directly administered. However, the patient in our case remained hemodynamically stable and made a full recovery with no noticeable neurological sequelae. It is possible that the pH of the rocuronium administered to this patient was buffered in the central nervous system or rendered less neurotoxic by dilution in the cerebrospinal fluid.

Neurotoxic action of a preservative or other excipient co-administered with rocuronium is also a concern when directly administered into the central nervous system. Preservatives have been shown¹⁵ to increase the risk of adverse neurological events. Some of the neuromuscular blockers have multidose vial presentations that contain benzyl alcohol (Table 3). Single-dose vial forms do not contain any preservative.

The rocuronium dose range for pediatric patients is 0.6 to 1.2 mg/kg/dose.¹⁶ Therefore, the amount administered to our patient, 6.3 mg/kg, was a clear overdose. In contrast to rocuronium, the normal dose of ropivacaine for caudal block in children is 2 mg/kg. If the anesthesiologist in our case had given 8 mL of 0.2% ropivacaine, 16 mg (1.3 mg/kg) would have been an appropriate dose for the patient. The average rocuronium duration of effect

after intravenous administration is 40 minutes in infants, 26 to 30 minutes in children, and 20 to 94 minutes in adults (prolonged in those >65 years of age).¹⁶ The duration of effect in our case is unknown because we did not conduct repeated train-of-four testing.

In a caudal injection, the needle is inserted near the tip of the tailbone into a small opening called the sacral hiatus. Once injected there, the drug can move from the epidural space through the meninges and into the cerebrospinal fluid or epidural fat. Some amount of the drug can then be picked up by local blood vessels that carry it into the systemic circulation system.¹⁷ Structurally, the non-depolarizing neuromuscular blockers are ionized monoquaternary (rocuronium, vecuronium) and bisquaternary (atracurium, cisatracurium, pancuronium) amines, increasing their hydrophilicity and dissolution into the aqueous cerebrospinal fluid.¹⁸ Under normal circumstances, the ionic nature of the quaternary amine and larger molecular size of rocuronium inhibit it from crossing the blood-brain barrier after intravenous administration. After epidural administration, however, rocuronium would not be expected to be retained for a prolonged period of time in the central nervous system fat or bound to protein. While the retention times in the central nervous system of rocuronium or the other neuromuscular blockers are unknown, they would be expected to be shorter than those of the local anesthetics that—while having smaller molecular weights—have higher lipid solubility and protein binding, chemical features that cause them to be retained in the central nervous system longer (Table 3).¹⁹⁻²¹ Chemically, rocuronium and the other non-depolarizing neuromuscular blockers would be expected to move into the more aqueous cerebrospinal fluid and then on into the systematic circulation via the epidural vertebral venous plexus or lymphatics. Depending on the dose administered, drug lipophilicity, and protein binding, the blood concentration that results after epidural injection is significant enough to produce complete neuromuscular blockade in some patients. In addition, pediatric patients, in general, have higher total cerebrospinal fluid volumes (infants, 4 mL/kg vs adults, 2 mL/kg) and higher spinal cerebrospinal fluid volumes (children, 50% vs adults, 33%) compared to adults. Therefore, a similar dose of rocuronium would be expected to have a lower central ner-

vous system concentration in children than in adults. Immature myelination (less barrier to drug diffusion), a more vascularized pia mater, and robust cardiac output in pediatric patients could possibly lead to faster onset and offset of neuromuscular blockers administered into the central nervous system as well, when compared with results in adult patients.²² The peak blood concentration after injection into the central nervous system would be expected to be delayed compared to intravenous administration, but not to the same extent as the local anesthetics. One case⁷ of accidental epidural injection of vecuronium showed a doubling of the recovery time from neuromuscular blockade after epidural administration, indicating a somewhat delayed release of the drug from the central nervous system compared to intravenous administration.

Non-depolarizing neuromuscular blockers are competitive antagonists of acetylcholine at nicotinic receptors found on the motor endplate at the neuromuscular junction of skeletal muscle. They are not known to bind to nicotinic receptors found in the brain or autonomic ganglion of the spinal cord. In our patient, a mild rise in heart rate without any change in blood pressure was seen after rocuronium injection. This increase in heart rate might indicate a small degree of cross reactivity by rocuronium at lumbar ganglion nicotinic receptors or perhaps it was due to other factors encountered in the case.

Neostigmine and pyridostigmine prolong the existence of endogenous acetylcholine by inhibiting acetylcholinesterase. This increases the amount of time during that acetylcholine molecules are available at the motor endplate, competing with the neuromuscular blocker. While acetylcholinesterase inhibitors reverse the skeletal muscle relaxation of non-depolarizing neuromuscular drugs, they are associated with unwanted cholinergic effects resulting from muscarinic receptor activation, such as bradycardia, bradyarrhythmias, increased secretions, and bronchoconstriction. Therefore, co-administration of an anticholinergic drug such as atropine or glycopyrrolate helps to attenuate these adverse effects and is often used to counteract the effects of acetylcholine at muscarinic sites.^{23,24} An acetylcholinesterase inhibitor and antimuscarinic anticholinergic were not co-administered in our patient because it was not thought to be necessary or advantageous to our patient's situation.

Further, this case of unintentional administration of rocuronium occurred prior to the launch of sugammadex in the United States. Sugammadex would have been an attractive alternative antidote for this patient, possibly promoting a faster recovery to spontaneous breathing.

Two case reports^{4,10} describe the administration of fluid to dilute the neuromuscular blocker in the epidural space or the administration of a corticosteroid as a rescue measure to reduce inflammation and edema. However, these interventions have not been established by evidence and could potentially worsen the situation by causing upward migration of the injected neuromuscular blocker. Therefore, we decided only to observe our patient and provide supportive treatment. We implemented controlled airway management, oxygen, and comfort drugs while monitoring hemodynamic stability, degree of muscle blockade, and neurological condition.

Finally, accidental administration of an unintended drug into the central nervous system can be associated with negative clinical effects to the patient and significant regret on the part of the clinician who administered the drug. In our case, the anesthesiologist selected the rocuronium vial from a matrix drawer of an automated dispensing machine that was not connected to an electronic prescribing system or health record. The dose was prepared without an independent double-check by another clinician, and the dose was administered without the use of a bar code system to verify the correct dose and patient combination. This case report emphasizes the importance of incorporating safety steps into the preparation and administration of epidural drugs as a part of a systemic approach to drug safety. Use of an electronic health record for operative doses incorporates synchronous dose and allergy checking and clinical decision support alerts. Use of the same system can effectively employ the use of bar code verification of vial contents prior to dose preparation and administration. An operating room-specific satellite pharmacy would be useful to offer independent verification of the drug order by a pharmacist and dose preparation by pharmacy staff in laminar flow conditions. Regardless of whether or not the dose is prepared in a pharmacy, an independent double-check of dose preparation and volume is an important step in ensuring correct drug selection and dose preparation. Finally, communication of drug er-

rors among providers both within and between health care institutions brings a personal story to the daily reality of the risks encountered in the drug use system and helps to sustain efforts directed at incrementally improving the safety of drugs in the operative setting.

Disclosure The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

Acknowledgments The authors wish to acknowledge Taro A. Tanaka, MD, for his advice in producing this manuscript.

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