Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

Date:	July 15, 2016
Safety Evaluator:	Martin Pollock, Pharm.D. Division of Pharmacovigilance II
Drug Use Analyst:	Tracy Pham, Pharm.D. Division of Epidemiology II
Team Leaders:	Sara Camilli, Pharm.D. Division of Pharmacovigilance II
	Rajdeep Gill, Pharm.D. Division of Epidemiology II
Deputy Director For Drug Utilization:	Grace Chai, Pharm.D. Division of Epidemiology II
Division Director (acting):	S. Christopher Jones, PharmD, MS, MPH Division of Pharmacovigilance II
Product Name(s):	Bloxiverz (neostigmine methylsulfate)
Pediatric Labeling Approval Date:	May 31, 2013
Application Type/Number:	NDA 204078
Applicant/Sponsor:	Eclat Pharms LLC.
OSE RCM #:	2016-453

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated post-marketing adverse event reports with a serious outcome and drug utilization data for Bloxiverz (neostigmine methylsulfate) injection in pediatric patients.

Bloxiverz was approved on 5/31/13 for use in adults and pediatric patients of all ages for the reversal of the effects of non-depolarizing neuromuscular blocking (NMB) agents after surgery.

The utilization data showed that approximately 14.8 million patients had a hospital billing for neostigmine injectable products over the cumulative time period from May 2013 through December 2015; of these, pediatric patients less than 17 years of age accounted for approximately 4% of total patients. We are unable to search the utilization data by product brand in our database; therefore, these hospital data are inclusive of all neostigmine injectable products, including Bloxiverz.

We found three FAERS cases during the first three years of neostigmine pediatric approval (5/31/13-3/29/16). The three cases reported the unlabeled event of pulmonary edema (PE). We found two additional PE cases in FAERS prior to the date of pediatric approval. All five FAERS cases were foreign literature reports and occurred in patients aged 1 to 16 years, whom all recovered. In all cases, PE occurred temporal to neostigmine administration and appeared to be non-cardiogenic. Two cases were confounded by prior respiratory or cardiac history. All cases can be considered confounded by potential airway management difficulties (e.g., broncho- and laryngospasm) that can occur in patients with advanced airway support.

Despite the confounding of the FAERS cases, based on the temporal association and known muscarinic effects of neostigmine, we cannot exclude neostigmine as a potential contributing factor to the PE reported in this case series. Patients receiving neostigmine in the post-operative setting are routinely closely monitored, facilitating appropriate detection and treatment of pulmonary edema, should it occur. Due to this close monitoring of patients and the therapeutic role for neuromuscular blocker reversal, the addition of pulmonary edema to neostigmine product labeling would likely not result in a meaningful impact on clinical practice. Thus, although we cannot completely exclude a causal role for neostigmine in this case series, we do not recommend regulatory action at this time.

We will continue routine monitoring for neostigmine.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Bloxiverz (neostigmine methylsulfate) was approved for use in adults and pediatric patients of all ages on 5/31/13 for the reversal of the effects of non-depolarizing neuromuscular blocking (NMB) agents after surgery.

As neostigmine was previously marketed as an unapproved product, the evidence for efficacy of neostigmine was derived from the published literature. Randomized, spontaneous-recovery of placebo-controlled studies using similar efficacy endpoints evaluated a total of 404 adult and 80 pediatric patients undergoing various surgical procedures. Patients had reductions in their recovery time from neuromuscular blockade with neostigmine methylsulfate treatment compared to spontaneous recovery.

Bloxiverz is available as a 0.5 mg/mL and 1 mg/mL 10 mL multiple-dose vial. The dose of neostigmine required to reverse neuromuscular blockade in children varies between 0.03 mg - 0.07 mg/kg, the same dose range shown to be effective in adults, and should be selected using the same criteria as used for adult patients.

Recovery of neuromuscular activity occurs more rapidly with smaller doses of cholinesterase inhibitors in infants and children than in adults. However, infants and small children may be at greater risk of complications from incomplete reversal of neuromuscular blockade due to decreased respiratory reserve.[1]

1.2 SUMMARY OF LABELED SAFETY ISSUES[1]

CONTRAINDICATIONS

- Hypersensitivity to neostigmine (4)
- Peritonitis or mechanical obstruction of the intestinal or urinary tract (4)

WARNINGS AND PRECAUTIONS

- Bradycardia: Atropine or glycopyrrolate should be administered prior to BLOXIVERZ to lessen risk of bradycardia. (5.1)
- Serious Reactions with Coexisting Conditions: Use with caution in patients with, coronary artery disease, cardiac arrhythmias, recent acute coronary syndrome or myasthenia gravis. (5.2)
- Neuromuscular Dysfunction: Can occur if large doses of BLOXIVERZ are administered when neuromuscular blockade is minimal; reduce dose if recovery from neuromuscular blockade is nearly complete. (5.4)

6 ADVERSE REACTIONS (select adverse events)

[1]From Bloxiverz label, last revised on 10/20/15.

6.1 Clinical Trials Experience (≥1%)

Respiratory, Thoracic and Mediastinal Disorders: dyspnea, oxygen desaturation <90%

6.2 Post Marketing Experience

Respiratory, Thoracic and Mediastinal Disorders: bronchospasm; increased oral, pharyngeal and bronchial secretions; respiratory arrest; respiratory depression

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

Proprietary databases available to the Agency were used to conduct the drug utilization analyses in this review (see Appendix A for full database descriptions and limitations).

2.1.1 Determining Settings of Care

Based on the IMS Health, IMS National Sales Perspectives™ database, nearly 100% of Bloxiverz vials were distributed to non-retail settings in 2015; of these, nearly 68% of Bloxiverz vials were distributed to non-federal hospitals.[2] As a result, Bloxiverz utilization patterns from non-federal hospital pharmacy setting were examined. Data from the outpatient retail and mail-order/specialty pharmacy settings are not included in this review.

2.1.2 Data Sources Used

The IMS Health, Inpatient HealthCare Utilization System database was used to provide national estimates of patients who had an inpatient or outpatient hospital discharge billing for neostigmine injectable products from U.S. non-federal hospitals from May 2013 through December 2015, cumulative. These data are stratified by patient age (0-16 and 17+ years). Because we are unable to search the data by product brand in this database, these hospital data are inclusive of all neostigmine injectable products, including Bloxiverz.

2.2 RESULTS

2.2.1 Number of Patients

[2] Source: IMS Health, IMS National Sales Perspectives™. Year 2015. Data extracted March 2016. File: NSP 2016-453 bloxiverz BPCA channel 3-24-2016.xlsx

Table 2.2.1. Nationally estimated number of patients with an inpatient or outpatient hospital discharge billing for neostigmine injectable products from U.S. non-federal hospitals, stratified by patient age*, from May 2013 through December 2015, cumulative

	Cumulative 5/2013-12/2015	
	Patients	***%***
Total Neostigmine Injectable	**14,783,571**	***100.0%***
0 - 16 years	653,730	*4.4%*
17+ years	14,132,271	*95.6%*

Source: IMS Health, Inpatient HealthCare Utilization System. May 2013 through December 2015. Data extracted March 2016. File: IHCARUS 2016-453 neostigmine BPCA all forms age 3-24-2016.xls

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years old (16 years and 11 months).

**Patient age subtotals may not sum exactly due to patients aging during the study period, and may be counted more than once in the individual age categories. For this reason, summing across patient age bands is not advisable and will result in overestimates of patient counts.

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in Table 3.1.1. See Appendix B for a description of the FAERS database.

Table 3.1.1 FAERS Search Strategy

Date of Search	3/29/16
Time Period of Search	5/31/13* – 3/29/16
Search Type	Quick Query
Product Names	Product active ingredient: neostigmine, neostigmine bromide, neostigmine methylsulfate
Search Parameters	All ages, all outcomes, worldwide

*Approval date of pediatric labeling and initial US approval date.

Based on the preliminary results of the search in Table 3.1.1, DPV also searched FAERS for additional serious cases of pulmonary edema in pediatric patients that were received prior to the

pediatric labeling date.[3] These additional cases will be discussed *outside*[4] of the pediatric cases series in Section 3.5.

3.2 RESULTS

3.2.1 Total number of FAERS reports by Age

Table 3.2.1 Total Adult and Pediatric FAERS Reports* from 5/31/13 to 3/29/16 with Neostigmine

	All reports (US)	Serious† (US)	Death (US)
Adults (≥ 17 years)	52 (21)	53(20)	4 (2)
Pediatrics (0 - <17 years)	5(0)	**5(0)**	0 (0)

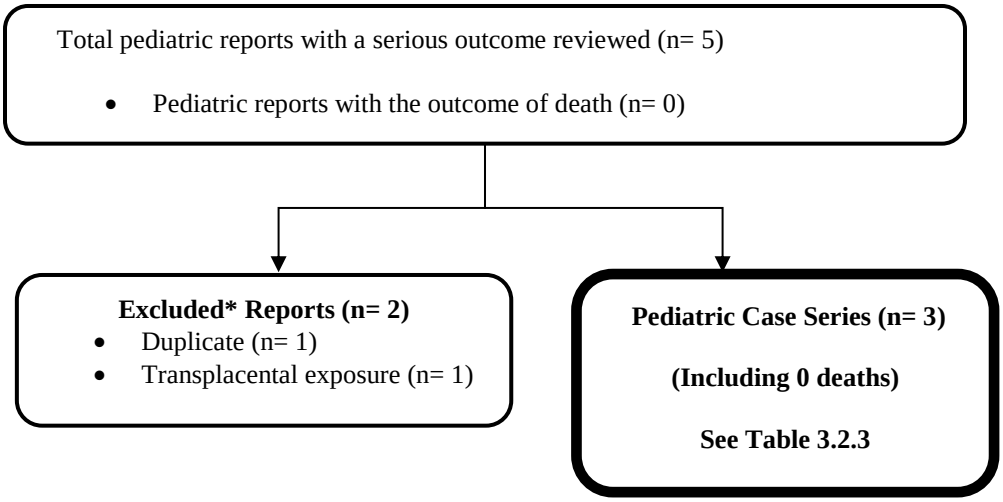
*May include duplicates and transplacental exposures, and have not been assessed for causality.
†Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.

3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified three pediatric reports with a serious outcome (See Table 3.2.1). See **Figure 3.2.2** below for the specific selection of cases to be summarized in **Sections 3.4 and 3.5.**

[3]Search parameters: time period 1/1/69 to 5/30/13: PTs: acute pulmonary edema, neonatal pulmonary edema, non-cardiogenic pulmonary edema and pulmonary edema.
[4]Will not be included in Figure 3.2.2 and Tables 3.2.3 and 3.4.

Figure 3.2.2 Selection of Serious Pediatric Cases with Neostigmine



* DPV reviewed these reports, but they were excluded from the case series for the reasons listed above

3.2.3 Characteristics of Pediatric Case Series

Appendix C lists all FAERS case and version numbers, Manufacturer Control Numbers and other information for the Pediatric Case Series.

Table 3.2.3 Characteristics of Pediatric Case Series with Neostigmine (N=3)[‡]

Age	1 year	2
	9 years	1
Sex	Male	3
Country	Foreign	3
	India	2
	Japan	1
Indication	NMB reversal	3
Serious Outcome[†]	Life-threatening	1
	Hospitalized	1
	Other serious	1

[‡]All cases were received as literature reports.
[†]Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.
Definition: NMB = neuromuscular blocker

3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=0)

There were no pediatric deaths in this case series.

3.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=3)

Of the three pediatric adverse event cases for neostigmine received in FAERS from 5/31/13 to 3/29/16, all reported the adverse event pulmonary edema (PE). One pulmonary edema case also reported anaphylaxis. Table 3.4 lists all reported adverse event terms in these three cases and the labeling status of each adverse event term.

Table 3.4 Non-Fatal Pediatric Serious Adverse Event Cases for Neostigmine: Listing of Adverse Event Preferred Terms[†] and Labeling Status (N=3)

SOC[†]	PT[†]	Labeling status	Number of Reports
Respiratory, thoracic and mediastinal disorders	Pulmonary edema	Not labeled	2
	Acute pulmonary edema	Not labeled	1
Investigations	Oxygen saturation decreased	Labeled	1
General disorders and administration site conditions	Crepitations	Not labeled	1
Immune system disorders	Anaphylactic reaction	Labeled	1

[†]Not mutually exclusive.
Definitions: SOC = system organ class; PT = preferred term.

Case narratives for the three pulmonary edema cases are described below. In all these cases (as well as those in Section 3.5), neostigmine was used for the labeled indication of NMB reversal. Our narratives focus on the available data near the time of neostigmine administration. In Appendix D, we list all other drugs administered before and during the surgical procedures and the dosage of neostigmine and the NMB, where known.

Case ID	10640523	Received date	12/5/14	Literature report?	Yes; Nagella 2014
Reported PTs:	Crepitations, oxygen saturation decreased, pulmonary edema				

A 1-year-old child had a palpable, undescended left testicle. He underwent diagnostic laparoscopy, open orchidopexy and circumcision. His medical history was 'unremarkable.' He had 'not suffered from an upper respiratory illness in the 3-week preceding surgery.' His pre-anesthesia exam was normal. The procedure lasted 90 minutes. 'ECG, SpO_2, $EtCO_2$, FiO_2 and inhalational agent concentration were monitored and found to be normal throughout surgery.'

After neuromuscular blocker (NMB) reversal with neostigmine,

> *the child was observed to have spontaneous respiratory efforts. A thorough oral suction was done. Just prior to extubation, pink, frothy secretions were noticed in the endotracheal tube. On auscultation, coarse crepitations were heard bilaterally in all lung areas. The oxygen saturation started dropping gradually and fell to less than 85%.*

'A diagnosis of pulmonary oedema was made.' Extubation was delayed. The child's treatment included reparalyzation, furosemide, hydrocortisone, and ventilation. He recovered and was discharged on post-op day 2.

The child had fasted for almost 10 hours before anesthesia induction. ECG, O_2 saturation, end tidal CO_2, temperature, inspired O_2 fraction were normal during surgery. Postoperative echocardiography showed no structural cardiac pathology.

The authors stated:

> *The present patient was healthy and had no pre-existing cardiorespiratory disease. Postoperative echocardiography revealed no structural cardiac pathology. Therefore, the possibility of cardiogenic pulmonary oedema was ruled out. The child had been fasting for almost 10 hours before induction of anaesthesia, thus, aspiration is unlikely to have occurred. He had not received any maintenance intravenous fluids during this period of fasting. Thus, the volume of intravenous fluid administered during surgery for replacement and maintenance was appropriate. This rules out fluid overload as the cause of pulmonary oedema.*
>
> *There were no signs suggestive of pulmonary oedema intraoperatively and all monitored parameters remained within normal limits. Ketamine-induced or laparoscopy-induced haemodynamic changes leading to pulmonary oedema would have manifested during surgery. Pink frothy secretions were first noticed in the endotracheal tube a few minutes after administration of glycopyrrolate and neostigmine at the end of surgery. At this point of time, the endotracheal tube was still in place and, therefore, upper airway obstruction (which could have caused negative pressure pulmonary oedema) did not cause pulmonary oedema in this patient.*

Other causes of NCPE [non-cardiogenic pulmonary edema] such as renal failure, sepsis, trauma, hyponatraemic encephalopathy were all ruled out. Based on the temporal sequence of the administration of the neostigmine plus glycopyrrolate mixture followed by the appearance of frothy secretions as well as the exclusion of all other causes, a diagnosis of neostigmine-induced pulmonary oedema was made.

Case ID	10876919	**Received date**	3/2/201	**Literature report?**	Yes; Wakana 2011
Reported	Anaphylactic reaction, pulmonary edema				

A 1-year-old male whose only medical history was congenital cataracts, underwent a 60 minute procedure for vitrectomy and lens reconstruction.

After the operation, inhalation anesthesia was stopped and ventilation endotracheal aspiration with pure oxygen was performed. 'There was no problem during the operation and the patient's respiration and circulation were stable. Immediately before the end of operation, dexamethasone (0.2 mL) was locally injected into both eyelids. After the operation, inhalation anesthesia was stopped and ventilation [and] endotracheal aspiration with pure oxygen was performed.'

Neostigmine was given for NMB reversal and then

> *Thereafter while performing several times of endotracheal aspiration, large amount of pink-colored foamy secretions began to be suctioned,[5] Chest X-ray revealed diffused infiltrative shadows in both lung fields. The patient was diagnosed as having pulmonary edema.'*
>
> Treatment included furosemide and 'artificial respirator under sedation with intubation and propofol.' The patient recovered.

The reporter also stated:

> *There was no preoperative finding suggesting respiratory infection and ventilation during operation was favorable. The patient had no previous history except congenital cataract; heart disorder was negative. Chest X-ray performed after operation showed no evidence of expansion of cardiac shadow and cardiogenic pulmonary oedema was negative. In addition, since intratracheal suctioning was possible after operation, pulmonary oedema due to intrathoracic negative pressure caused by airway closure was also negative. His vital signs were stable during the operation and until before initiation of the intratracheal suctioning and possibility of aspiration was considered low (no vomitus was suctioned).*

[5]The lab data in the report lists four pO_2 values ranging from 140 to 333 Torr, all dated the same day as the event. All data was missing time points, therefore, we cannot correlate these pO_2 values to the clinical events. Normal pO_2 is 83 to 103 Torr. Therefore these reported elevated values are most likely due to the patient receiving external oxygen.

Since there was no abnormality during the operation, drug-induced pulmonary oedema caused by dexamethasone sodium phosphate[6] or neostigmine methylsulfate (VAGOSTIGMIN) which were used right before the completion of operation was suspected.

The reporter also stated that in addition to pulmonary edema, 'drug-induced anaphylaxis was considered to be the cause.' However, there was no mention of the presence of anaphylactic-associated symptoms such as skin reactions, increased heart rate, and airway constriction. The physician also stated that a 'drug allergy test had not been performed.'

Case ID	11235501	**Received date**	12/5/14	**Literature report?**	Yes; More 2015
Reported	Acute pulmonary edema				

A 9-year-old male child, with history of 'chronic tonsillitis,' underwent a tonsillectomy. 'Adequate starvation' was confirmed before the procedure.

ECG and pulse oximetry were normal during the 45-minute procedure. He was suctioned, then given neostigmine for NMB reversal and extubated ($Sp0_2$ 98%). The patient 'was still on the table and he developed tachypnoea, restless and wet cough with pink frothy sputum and oxygen saturation of 92%.' He received O_2; chest auscultation showed bilateral crepitations. He was reintubated with 'intermittent positive pressure ventilation because of respiratory distress.' He was given hydrocortisone, dexamethasone, theophylline, furosemide and vecuronium and underwent urinary catheterization. He improved with stable vitals and O_2 saturation 30 minutes later.

He was given neostigmine for the second time[7] and 'again experienced pink frothy secretions through endotracheal tube and he was coughing and biting on the tube.' He received atracurium and 'his chest auscultation again showed bilateral crepitations.' He was treated with aminophylline, chlorpeniramine, and theophylline and did recover.

The authors stated:

The muscarinic side effects [of neostigmine] are increased salivation, excessive bronchial secretions, bronchospasm, increased intestinal motility, bradycardia, conduction block (sinus node depression, atrio-ventricular block). The pulmonary side-effects viz. bronchospasm, bronchiolar constriction and increased bronchial secretions could lead to pulmonary oedema.

[6] 0.2 mL not otherwise specified, locally injected into each eye lid.
[7] Both neostigmine administrations were within recommended; the NMB (vecuronium both times) dosage was not reported (Appendix D).

Hence we conclude that the likely cause for postoperative acute pulmonary edema was due to neostigmine, however NPPE[8] (type 2) following relief of upper airway obstruction, post tonsillectomy, cannot be ruled out.

3.5 ADDITIONAL SERIOUS PEDIATRIC CASES OF PULMONARY EDEMA REPORTED TO FAERS PRIOR TO THE PEDIATRIC LABELING DATE (N=2)

We found two additional serious cases of pulmonary edema in pediatric patients exposed to neostigmine reported to FAERS prior to the pediatric labeling date (5/31/13).[9]

Case ID	9240142	**Received date**	4/17/13	**Literature report?**	Yes; Cordery 2006
Reported PTs:	Brugada syndrome, bundle branch block right, confusional state, electrocardiogram ST segment abnormal, hypertension, hypoxia, laryngospasm, low cardiac output syndrome, metabolic acidosis, posturing, pulmonary oedema, pulse absent, respiratory distress, sinus tachycardia				

A 'previously healthy' 16-year-old male experienced respiratory distress at his home; his mother 'felt no pulse.' Paramedics diagnosed ventricular fibrillation and performed cardiac resuscitation which restored sinus rhythm. The patient arrived at the hospital with tachycardia, hypertension, Glasgow score of 9 and 'decorticate posturing.' He was intubated and ventilated. ECG showed sinus tachycardia, incomplete right bundle-branch block and anterior ST-segment abnormality. There was metabolic acidosis 'assumed to be secondary to the period of low cardiac output.' In light of this teenager's 'ventricular fibrillation arrest' the report stated that 'a presumptive diagnosis' of *Brugada syndrome* was made.[10]

Therefore, the patient underwent a 90-minute procedure for an implantable cardioverter defibrillator. After NMB reversal with neostigmine,[11] spontaneous ventilation returned, and the patient was extubated.

At this point, his arterial oxygen saturation decreased. There was a brief period of laryngeal spasm, which resolved with a small amount of continuous positive-airway pressure. However, he also developed excessive pink frothy sputum consistent with pulmonary edema. An urgent chest radiograph confirmed the pulmonary edema and confirmed the correct placement of the ICD lead. Transthoracic echocardiography excluded a pericardial collection.

[8]NPPE means negative pressure pulmonary edema. 'Type 2' refers NPPE occurring *after* relief of an airway obstruction; 'Type 1' has occurs *before* relief of the obstruction (More 2015).
[9]Four reports were retrieved; two were determined to be duplicates.
[10]'Brugada' is believed to be a genetic disorder resulting in abnormal cardiac conduction; outcomes range from asymptomatic to sudden cardiac death (Veerakul 2012). The patient (Case ID 9240142) was given phenytoin upon arrival at the hospital as a precaution for seizures. The phenytoin prevented the physicians from administering the 'ajmaline [class 1A antiarrhythmic] challenge' which is used to diagnose Brugada (Arnalsteen 2010). However, the patient's father who had an abnormal ECG did have a positive ajmaline challenge implying Brugada. Father and son are of Southeast Asian (Filipino) descent whom are known to have higher incidences of Brugada (Cordery 2006).
[11]Neostigmine and NMB (vecuronium) dosage was within recommended; NMB (atracurium) was not reported.

The patient was treated with intermittent positive airway ventilation and diuretics. The patient recovered, after which the authors stated:

> *A differential diagnosis of negative-pressure pulmonary edema (secondary to laryngeal spasm) and ventricular dysfunction as a result of his recent arrest were considered. At this point, the authors had not considered the muscarinic effects of neostigmine.*

Concerning neostigmine and other causal factors, the authors concluded:

> *Neostigmine administration may have increased parasympathetic drive in this patient and induced discordance between right and left ventricular contraction to trigger increased left atrial pressures and pulmonary edema. Therefore, it may be advisable to avoid the use of all muscarinic drugs in these patients. In this case, laryngeal spasm also complicated reversal of anesthesia and extubation. It is therefore impossible to determine if the pulmonary edema occurred because of negative pressure, parasympathetic stimulation and subsequent myocardial dysfunction, or a combination of both.*

Case ID	7921061	**Received date**	4/6/11	**Literature report?**	Yes; Raiger 2010
Reported PTs:	Irritability, non-cardiogenic pulmonary edema				

A 6-year-old male child who had an 'unremarkable PAE [pre-anesthesia evaluation]' and had fasted overnight underwent a procedure for corneal repair. Vital signs were stable throughout the surgery.

Three minutes after NMB reversal with neostigmine,[12]

> *The patient was fully conscious, opening eyes, had spontaneous respiration with adequate tidal volume, having good muscle power and not tolerating the tube so he was extubated. During that time SpO2 couldn't be recorded because patient was moving vigorously…. after extubation he was irritable, crying and not allowing to keep mask on the face for oxygenation. BP was 100/60, HR 130/min, SpO2 70%, normal ECG, auscultation of chest showed crepts. Immediately propofol and atracurium were given and on laryngoscopy, frothy secretions were seen at the laryngeal inlet. He was reintubated ……and ventilated with 100% O2 ……..Copious pink frothy secretions coming out through the tube were suctioned frequently.*

The patient was 'propped up,' catheterized and given steroids (NOS), theophylline and furosemide. The patient recovered. The authors concluded:

> *Although, we could not find any drug induced NCPE [non-cardiogenic pulmonary edema] reported after neostigmine in literature or Internet search; in our opinion, the cause of this pulmonary oedema was drug-induced NCPE.*

[12]Neostigmine dosage was within recommended; NMB (vecuronium) dosage.

4 DISCUSSION

The utilization data showed that approximately 14.8 million patients had a hospital billing for neostigmine injectable products over the cumulative time period from May 2013 through December 2015; of these, pediatric patients less than 17 years of age accounted for approximately 4% of total patients. Of note, we are unable to search the utilization data by product brand in our database; therefore, these hospital data are inclusive of all neostigmine injectable products, including Bloxiverz.

The drug utilization data focus on only the non-federal hospital pharmacy settings; therefore, these estimates may not apply to other settings of care such as clinics in which neostigmine injectable products may be used. The IMS Hospital CDM sample does not include Federal hospitals, including VA facilities, and some other specialty hospitals (including children's hospitals and other standalone specialty hospitals), and does not necessarily represent all acute care hospitals in the U.S. in all markets. Therefore, these data may not apply to utilization patterns in specialty hospitals such as standalone children's hospitals where neostigmine injectable products may be used.

PE can be classified as two types: cardiogenic and *non*-cardiogenic (Ware 2005).[13] For a cardiogenic PE diagnosis, the patient will have some type of cardiac dysfunction before or concurrent with the event. With the exception of Cordery 2006, all FAERS cases did not report any such cardiac abnormalities. Therefore, the PE in at least four of the five cases appeared to be non-cardiogenic (NCPE). NCPE may also be called *post obstructive*, *negative pressure,*[14] and *laryngospasm induced pulmonary edema* (McConkey 2000). The genesis of NCPE is thought to be airway obstruction followed by inspiration against a closed airway which produces negative intrathoracic pressure. Intrapleural and transpulmonary pressure gradients then become negative. This results in movement of fluid from the pulmonary capillaries (via increased permeability) to the interstitial fluid and into the lungs (Miller 1995). All FAERS cases reported at least two out of three symptoms/findings that are associated with NCPE: respiratory distress (e.g., O_2 desaturation), hemoptysis (e.g., 'pink colored secretions') and lung infiltration (via X-ray) (McConkey 2000).

One FAERS case was confounded by cardiac disease (Cordery 2006). The authors acknowledge that in addition to neostigmine's temporal relationship and parasympathetic stimulation, two other significant contributing factors were laryngospasm and the patient's cardiac (Brugada) disease; we agree.[15] In the remaining four cases, there was a temporal relationship to neostigmine administration, clinical stability (via vital signs and other cardio-respiratory monitoring) before the PE, and absence of prior cardiac history. From this, two authors (Nagella

[13]The literature describes some PE cases as *Neurogenic* (NPE). NPE is thought to be generated by (in order of occurrence) central sympathetic discharge, systemic and pulmonary vasoconstriction, increased pulmonary hydrostatic pressure, increased pulmonary capillary permeability, resulting in PE. NPE is usually seen in patients with neurologic pathology e.g. subarachnoid hemorrhage, brain injury, stroke, hydrocephalus and seizures—all of which none of our FAERS cases had. NPE has characteristics of *cardiogenic* (hydrostatic) and *non-cardiogenic* (capillary permeability) PE, Therefore, NPE is not considered to in a PE class by itself (Busl 2015, Murray JF 2011).

[14]We use *negative pressure pulmonary edema* (NPPE) *and non-cardiogenic pulmonary edema* (NCPE) *interchangeably.*

[15]Cordery 2006 calls the patient's PE NPPE. However in light of the patient's Brugada history and symptoms, one could consider this a cardiogenic PE case. In either case, neostigmine's role remains minimal.

2014 and Raiger 2010) concluded that neostigmine was responsible for the NCPE and two (More 2015 and Wakana 2011) concluded that neostigmine was one of two factors responsible; other factors deemed potentially contributory by the authors include tonsillectomy (Feinberg 1985) and concomitant dexamethasone, respectively.

The neostigmine labeling includes bronchospasm and increased pharyngeal and bronchial secretions as adverse events in the Postmarket Experience subsection. This is not surprising because neostigmine administration results in muscarinic receptor activation which can stimulate respiratory tract contraction and secretions. This can result in broncho- and laryngospasm (Morgan and Mikhail 2013). Most (4/5) FAERS cases[16] were also given a concomitant anticholinergic (glycopyrrolate) in order to minimize neostigmine's muscarinic effect. Even so, it is possible that there still was some unopposed muscarinic activity. Therefore, we acknowledge that neostigmine could have been a causal factor in our case series of pulmonary edema adverse events.

Although rare, NCPE can be a consequence for *any* patient undergoing anesthesia with an advanced airway; incidence is estimated to be 0.1% (McConkey 2000). Airway spasms (e.g., laryngo- and bronchospasm) can occur during anesthesia and lead to NCPE (Ead 2003). The occurrence of airway spasms with premature extubation or aggressive endotracheal tube suctioning is a risk of advanced airway management, independent of any particular anesthetic drugs administered, such as neostigmine. Although an infant with limited respiratory reverse capacity can have a more challenging recovery from NCPE, healthy patients of all ages can experience postoperative NCPE. Interestingly, there is thought to be a higher risk of postoperative NCPE in male athletes because of their stronger respiratory drive and ability to generate the highest negative inspiratory pressures when an airway obstruction is present (Bhattarai 2011, Tarrac 2003).

Although our case series is limited to pediatric patients, there are also literature reports of NCPE post-neostigmine administration in *adults.* Raiger 2010, in addition to the 6 year-old in our case series, reports a case of pulmonary edema in a 45 year-old male who underwent haemangioma excision on the lower lip. In addition, Bhattarai 2011 reports a case of pulmonary edema in a 35 year-old who had a procedure for repairing a humerus fracture. Both of these patients had normal preoperative evaluations.[17] Therefore, a potential association of neostigmine with PE does not appear to be unique to pediatric patients.

5 CONCLUSION

The utilization data showed that approximately 14.8 million patients had a hospital billing for neostigmine injectable products over the cumulative time period from May 2013 through December 2015; of these, pediatric patients less than 17 years of age accounted for approximately 4% of total patients.

[16]Wakana 2011 had no mention of a concomitant anticholinergic.
[17]'No relevant past medical history for 35 year-old, other than he was a 'snorer'. No mention of medical history for 45 year-old.

We found three FAERS cases during the first three years of neostigmine pediatric approval (5/31/13-3/29/16). The three cases reported the unlabeled event of PE. We found two additional PE cases prior to the pediatric approval. All five cases were foreign literature reports and occurred in patients aged 1 to 16 years, whom all recovered. In all cases, PE occurred temporal to neostigmine administration and appeared to be non-cardiogenic. Two cases were confounded by prior respiratory or cardiac history. All cases were confounded by potential airway management difficulties (e.g., broncho- and laryngospasm) that can occur in patients with advanced airway support.

Despite the confounding of the cases, based on the temporal association and known muscarinic effects of neostigmine, we cannot exclude neostigmine as a potential contributing factor to the PE reported in this case series.

6 RECOMMENDATIONS

Patients receiving neostigmine in the post-operative setting are routinely closely monitored, facilitating appropriate detection and treatment of pulmonary edema, should it occur. Due to this close monitoring of patients and the therapeutic role for neuromuscular blocker reversal, the addition of pulmonary edema to neostigmine product labeling would likely not result in a meaningful impact on clinical practice. Thus, although we cannot completely exclude a causal role for neostigmine in this case series, we do not recommend regulatory action at this time. We will continue routine monitoring for neostigmine.

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8 APPENDICES

8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IMS, Inpatient HealthCare Utilization System (IHCarUS)

IMS longitudinally tracks patient-level diagnoses, procedures, and drug utilization within hospitals (inpatients and outpatients). The Charge Data Master (CDM) is a collection of data streams that is large, well distributed, and geographically representative. IMS collects and maintains patient-level hospital inpatient and hospital outpatient (including all ED) setting data from more than 630 hospitals, covering each census region of the United States (US), including all inpatient hospital and outpatient (including ED) hospital patient level records. The hospital data is collected electronically on a weekly and monthly basis from hospital CDM patient level records. Data fields collected include diagnoses, procedures, drugs (i.e., ingredient name, brand name, strength, and daily administrations), and location of each service and room type (e.g. Pediatric ICU) by day of stay The hospital inpatient and outpatient patient records are linked longitudinally through unique patient-level IDs. The lag time between the hospital encounter date and availability of IMS' hospital inpatient and hospital outpatient raw and projected hospital data and reporting is 25-30 days.

The IMS Hospital CDM sample does not include Federal hospitals, including VA facilities, and some other specialty hospitals (including children's hospitals and other standalone specialty hospitals), and does not necessarily represent all acute care hospitals in the U.S. in all markets. Caveats of the IMS CDM data source are common to this type of hospital charge information, but are mostly limited to limitations of charge descriptions and what is actually entered by the sample hospitals. However, validations of IMS' Hospital CDM data using both the National Hospital Discharge Survey (NHDS) and the AHRQ HCUP data have shown IMS' patient level data to be representative and accurate across multiple therapeutic areas.

8.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.3 APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES AND ADDITIONAL CASES OF PEDIATRIC PULMONARY EDEMA WITH NEOSTIGMINE (N=5)

	Search period				
Case ID - Version #	5/31/13 to 3/29/16	1/1/69 to 5/30/13	**Country**	**Mfr control #**	**Reference**
10640523-1	x		India	2014ECL00014	Wakana 2011
10876919-1	x		Japan	JP-009507513-1109USA00400	More 2015
11235501-1	x		India	IN-FRESENIUS KABI-FK201503125	Cordery 2006
9240142-1		x	England	1672883	Nagella 2014
7921061-2		x	India	FRK201100537	Raiger 2010

8.4 APPENDIX D. PEDIATRIC CASE SERIES: MEDICATIONS ADMINISTERED BEFORE AND DURING THE PROCEDURE AND DOSING FOR NEOSTIGMINE AND NMB*

Literature reference	Nagella 2014	Wakana 2011	More 2015	Cordery 2006	Raiger 2010
Case ID	10640523	10876919	11235501	9240142	7921061
Drug					
NMB reversed:					
Atracurium	x^			x	x
Vecuronium		x	x†		
Other drugs					
Midazolam	x		x		x
Succinylcholine‡			x		
Thiopental			x		x
Sevoflurane	x	x		x	
Nitrous oxide	x	x	x		
Halothane			x		
Propofol				x	x
Fentanyl	x			x	
Ketamine	x				
Succinylcholine			x		
Tramadol					x
Pentazocine			x		
Glycopyrrolate	x		x#	x	x
Fosfomycin♦		x			
Metoclopramide			x		
Ondansetron					x
Diclofenac					x
Dexamethasone sodium phosphate		x			
Fluid volume given during operation (ml)	150	200	250	1500	240
Neostigmine dose (mg/kg)	0.0625	0.0009	0.067(1st dose) 0.033 (2nd dose)	0.040§	0.067

NMB dose (mg/kg) within labeled dosage range‖	0.625;^ above	0.09; yes	Unknown for both vecuro-nium admni-	0.49; yes	Unknown

*Neuromuscular blocker
†Given twice and reversed with neostigmine each time.
#Given twice, with each neostigmine administration.
^Other 'intermittent' (unknown) doses also given.
‡Succinylcholine was given as induction and 'premedication' respectively. With its short $t_{1/2}$ and duration we would not expect to be an issue when neostigmine was given for the reversal of the *non-depolarizing* NMB at the end of the procedure.
♦Given 'iv drip'; only available orally in U.S.
§2.5 mg given to a 'previously healthy' 16-year-old of unknown weight. We estimate weight to be 61 kg (Center for Disease Control and Prevention 2000).
‖Atracurium: adult: 0.4-0.5 mg/kg; children up to 2 yrs: 0.3 to 0.4 mg/kg;[18] Vecuronium 0.08 to 0.1 mg/kg; adult or pediatrics.

[18]Label sources: atracurium (Baxter Healthcare Corp) revised 5/2006; vecuronium (Teva Parenteral Medicines Inc) revised June, 2015.

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/s/

MARTIN L POLLOCK
07/15/2016

TRACY M PHAM
07/15/2016

SARA L CAMILLI
07/15/2016

RAJDEEP K GILL
07/15/2016
Drug use data has been cleared by data vendors.

GRACE CHAI
07/18/2016

STEVEN C JONES
07/19/2016