**CLINICAL VIGNETTE**

# Bethanachol Induced Cholinergic Toxicity

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## *Introduction*

Bethanechol, a parasympathomimetic cholinergic agonist, binds selectively to muscarinic receptors (M1-M5) but not nicotinic receptors, in contrast to acetylcholine, which has affinity to both receptors. In addition to its selective properties, bethanechol is relatively stable and does not undergo degradation by acetylcholinesterase prolonging therapeutic duration. Bethanechol has been used to treat xerostomia as a sialagogue, for treatment of neurogenic bladder and nonobstructive and post-partum urinary retention. Cholinergic toxicity can lead to parasympathetic stimulation of multiple organ systems, including gastrointestinal, cardiac, respiratory, central nervous system (CNS), integumentary, and genitourinary systems.[1,2] This case illustrates the diagnosis and management of bethanechol induced cholinergic toxicity in an acute rehab patient with neurogenic bladder.

## *Case Report*

A 27-year-old male with sickle cell trait, tobacco and marijuana use presented after a transcontinental flight and long drive with sudden headache followed by obtundation with agonal breathing. CTA imaging revealed a non-traumatic large parenchymal hemorrhage with ventricular extension. He was intubated and taken to the OR for suboccipital craniotomy. His hospital course was complicated by stress-induced cardiomyopathy, cerebral edema, aspiration pneumonia, dysphagia requiring PEG placement, myoclonus and urinary retention. He was discharged to acute rehab with foley catheter.

In acute rehab, he failed his voiding trial after his first week. Urology was consulted and he was initiated on bethanechol 25 mg three times daily for neurogenic bladder. He developed nausea, vomiting and loose and nocturnal stools 5 days after bethanechol had been introduced. C. difficile PCR test returned negative. His symptoms had been attributed to prior marijuana use with concern for cyclical vomiting and to his tube feeding which prompted temporary discontinuation followed by several decreased rate trials throughout the week. He was also started on ondansetron. The rapid response team was called 7 days after bethanechol was started for acute abdominal pain, respiratory distress and copious diarrhea.

Borborygmi was audible upon entrance to the room. Bedside evaluation, noted increased lacrimation, miosis, hypersalivation, diaphoresis, flushing, and profuse diarrhea and urination. Patient complained of abdominal cramping, nausea and shortness of breath. Auscultation demonstrated diffuse wheezing and bradycardia to the 40s. Discussion with nursing revealed that nighttime medications, including bethanechol had been given one hour prior to onset of his acute symptoms.

He was treated with albuterol/ipratropium nebulizers for coughing, bronchospasm and placed on nonrebreather mask. Bethanechol was stopped. Atropine 0.6 mg was given subcutaneously, as he did not have IV access, with reversal of all symptoms within one hour.

## *Discussion*

Acetylcholine, the main neurotransmitter involved in parasympathetic physiology, acts on muscarinic and nicotinic receptors found on a wide array of tissues. The parasympathetic nervous system (PNS) allows the body to return to homeostasis after stressful situations, colloquially thought of as “rest and digest”. Functions of the PNS include decreasing heart rate and cardiac output; ciliary muscle constriction which allows for near vision; increased lacrimal and salivary glandular secretions; gut promotility, secretory stimulation and relaxation of gut sphincter tone; bronchoconstriction of airways, urethral sphincter relaxation and contraction of detrusor muscle of the bladder for micturition; glycogen synthesis; as well as activation of the immune system.[3] Blood vessels generally do not have PNS innervation aside from glandular tissues mentioned, coronary arteries and genital erectile tissue where they promote vasodilation.[4]

Supratherapeutic levels of medications, drugs, and other substances may imitate the neurotransmitter acetylcholine, activate the acetylcholine receptor or inhibit the enzyme acetylcholinesterase result in cholinergic toxicity. Depending on the excess of cholinergic substances at the neuromuscular junction, parasympathetic hyperstimulation may develop immediately or have delayed onset allowing for a toxidrome to ensue. Commonly, the muscarinic toxidrome is referred to as DUMBELS (defecation, urination, miosis, bronchorrhea/bronchospasms/bradycardia, emesis, lacrimation and salivation). Nicotinic effects of toxicity would include fasciculations, muscle weakness and paralysis commonly seen with succinylcholine when administered for operative cases. Other CNS effects of cholinergic toxicity induced lethargy, headaches, confusion and slurred speech, respiratory depression and coma. If left un-

treated cholinergic toxicity may result in death via cardio-pulmonary arrest with fatality rate estimated at 15%.[5,6]

Treatment of acute cholinergic toxicity depends on the suspected etiology of cholinergic excess. Atropine sulfate is a reversible competitive antagonist of muscarinic receptors located in the post-ganglionic areas of the vagal nerves resulting in a direct vagolytic response. Oximes, such and pralidoxime chloride, work to reactivate acetylcholinesterase that had been constrained by organophosphates. In cases of organophosphate/ insecticide poisoning both muscranic and nictonic receptors are affected, and treatment includes basic life support and IV atropine 1-3 mg as a bolus followed pralidoxime chloride 2 g IV and repeating doses of atropine as indicated every 5 minutes until heart rate reaches greater than 80 bpm. Pralidoxime infusions are continued until the patient has not required atropine for 12-24 hours. Benzodiazepines may be administered for agitated delirium and seizures.[6,7] Bethanechol toxicity, atropine sulfate is recommended for adults at an initial dose of 0.6 mg given IV or subcutaneously. It may be repeated every 2 hours until achievement of therapeutic response.[8]

***Conclusion***

Bethanechol is a relatively stable muscarinic receptor agonist that is commonly used for treatment of neurogenic bladder, overflow incontinence and post-partum/postoperative urinary retention and less commonly as a sialagogue. Symptoms of toxicity should be closely monitored, and medication should be held if there is any concern for adverse effects. In cases of toxidrome and acute toxicity, atropine sulfate 0.6 mg may be administered intravenously or subcutaneously and repeated every 2 hours until symptom resolution. Special attention should be paid to cardiopulmonary systems and basic life support should be provided as needed.

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