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Cholinergic Crisis in an Older Adult Patient With Severe Constipation Receiving Distigmine and Bethanechol: A Case Report

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 84-year-old
Final Diagnosis: Cholinergic crisis
Symptoms: Impaired consciousness
Clinical Procedure: —
Specialty: Critical Care Medicine

Objective: Unknown etiology

Background: Cholinergic crisis is a life-threatening condition caused by excessive cholinergic stimulation. Distigmine, a cholinesterase inhibitor, and bethanechol, a cholinergic agonist, are both used to treat neurogenic bladder and are occasionally prescribed together. Although both agents can cause cholinergic toxicity, it remains unclear whether clinical conditions such as severe constipation may contribute to severe cholinergic crisis.

Case Report: An 84-year-old man with chronic constipation was transported to the emergency department because of impaired consciousness. Distigmine (5 mg/day) had been started 3 months before admission, and bethanechol (45 mg/day) had been added approximately 1 month before admission. On arrival, the patient was comatose with severe bradycardia, shock, respiratory failure, and prominent cholinergic manifestations. Laboratory test results showed renal dysfunction and markedly reduced serum butyrylcholinesterase activity. Abdominal computed tomography demonstrated severe fecal retention extending from the descending colon to the rectum. Based on the characteristic cholinergic manifestations, medication history, and low serum butyrylcholinesterase activity, cholinergic crisis induced by combined distigmine and bethanechol therapy was diagnosed. The patient required intensive care, including mechanical ventilation, norepinephrine and vasopressin infusions, and continuous atropine administration. His condition gradually improved and he was discharged on day 77.

Conclusions: Severe constipation may represent an additional contributor to cholinergic toxicity in older adults receiving combined cholinergic therapy for neurogenic bladder. Although causality cannot be established in a single case, careful assessment of bowel status and other risk factors is warranted when prescribing cholinergic agents.

Keywords: Cholinergic Agents • Cholinesterase Inhibitors • Constipation • Poisoning

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Introduction

Excretory dysfunction, including chronic constipation and voiding dysfunction, is common in older adults and is associated with reduced activities of daily living and an increased risk of infection [1,2]. Prolonged gastrointestinal transit time, such as that caused by constipation, has been recognized as one of the factors that may influence the pharmacokinetics of orally administered drugs. However, whether severe constipation contributes to clinically significant drug toxicity remains unclear [3].

Pharmacological therapies for neurogenic bladders with detrusor underactivity may include cholinesterase inhibitors and cholinergic agonists to facilitate voiding [4]. Cholinesterase inhibitors indirectly enhance parasympathetic activity by inhibiting cholinesterase and increasing acetylcholine at synapses, whereas cholinergic agonists directly stimulate muscarinic receptors. Cholinesterase inhibitors and cholinergic agonists both carry a risk of cholinergic crisis, a life-threatening condition caused by excessive cholinergic stimulation, and their combined use may further increase this risk. However, because neurogenic bladder is often caused by irreversible neurological disorders, treatment efficacy is frequently limited, and combination therapy may be required to achieve adequate symptom control [4].

We report a case of life-threatening cholinergic crisis in an older patient. The patient had not developed a cholinergic crisis even while receiving distigmine and bethanechol, but ultimately developed the crisis accompanied by severe constipation. This case raises the possibility that severe constipation can contribute to cholinergic toxicity during combination therapy.

Case Report

An 84-year-old man with impaired consciousness was transported to our emergency department. His medical history included hypertension, dyslipidemia, insomnia, dementia, benign prostatic hyperplasia, and a history of surgery for a compression fracture of the 11th thoracic vertebra. He also had neurogenic bladder and chronic constipation. He had no known renal dysfunction before admission. He had no history of smoking or alcohol consumption, and had no known allergies. He resided in a nursing facility and was independent in most activities of daily living. His medications were managed by the nursing facility staff, and according to the facility, his regularly prescribed medications were administered through the morning of admission.

The patient had been treated for chronic constipation with laxatives and probiotics for several years. He was also receiving an α-adrenergic receptor antagonist and a phosphodiesterase-5 inhibitor for benign prostatic hyperplasia. Approximately 3 months before admission, he received a diagnosis of neurogenic bladder with detrusor underactivity at a local urology clinic because of urinary incontinence and an increased post-void residual volume, and treatment with distigmine (5 mg/day) was initiated. Approximately 1 month before admission, bethanechol (45 mg/day) was added because of persistent voiding dysfunction and increased post-void residual volume. Although his urinary symptoms improved, management of chronic constipation remained challenging. He had been in his usual state of health without any apparent symptoms until the day before admission. On the day of admission, he was found in a restroom with impaired consciousness and was transported to our hospital.

On arrival, his Glasgow Coma Scale score was 3 (E1V1M1), body temperature was 36.5 °C, heart rate was 30 beats/min, blood pressure was unmeasurable, and oxygen saturation was 90% with bag-valve-mask ventilation at 10 L/min oxygen. Pupillary diameter was 3 mm bilaterally, and the pupillary light reflex was sluggish. Weak radial pulses and cold extremities suggested circulatory failure. Marked lacrimation, hypersalivation, excessive airway secretions, and generalized diaphoresis suggested parasympathetic overactivity. Cardiac examination revealed regular rhythm without murmurs. Breath sounds were clear bilaterally without wheezing or crackles. The abdomen was soft and flat, with increased bowel sounds.

Blood gas analysis revealed metabolic acidosis and elevated lactate levels. Laboratory examination revealed renal dysfunction with a blood urea nitrogen level of 21.0 mg/dL and a serum creatinine level of 1.42 mg/dL. Serum butyrylcholinesterase activity was markedly decreased to 32 U/L (reference range, 240-486 U/L) (**Table 1**). Abdominal computed tomography revealed severe fecal retention extending from the descending colon to the rectum along with fluid retention and niveau formation in the small intestine (**Figure 1**). No other significant abnormalities were detected on further examination.

Clinical examination and diagnostic testing revealed no evidence of hemorrhagic, cardiogenic, or obstructive shock, suggesting a distributive mechanism. Sepsis was considered unlikely because the patient was afebrile, his C-reactive protein level was low, computed tomography showed no evidence of an infectious source, and his cultures remained negative. His characteristic cholinergic manifestations and markedly decreased serum butyrylcholinesterase activity supported the diagnosis of cholinergic crisis. Organophosphate poisoning was unlikely because the patient resided in a nursing facility and had no known exposure. Because his medications were administered by facility staff, accidental overdose or other drug intoxication was unlikely. Therefore, distigmine and bethanechol were considered the most likely causative agents.

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Table 1. Laboratory findings on admission. Laboratory test results showed renal dysfunction, markedly decreased serum butyrylcholinesterase activity, and metabolic acidosis with hyperlactatemia.

Parameter	Value	Reference range
Hematology		
White blood cell count (× 10^3/μL)	12.5	3.3-8.6
Hemoglobin (g/dL)	13.2	13.7-16.8
Platelet count (× 10^3/μL)	173	158-348
Blood Chemistry		
Urea nitrogen (mg/dL)	21.0	8.0-20.0
Creatinine (mg/dL)	1.42	0.65-1.07
Aspartate aminotransferase (U/L)	23	13-30
Alanine aminotransferase (U/L)	17	10-42
Lactate dehydrogenase (U/L)	189	124-222
Butyrylcholinesterase (U/L)	32	240-486
Sodium (mEq/L)	140	138-145
Potassium (mEq/L)	2.9	3.6-4.8
Chloride (mEq/L)	108	101-108
Creatine kinase (U/L)	110	59-248
C-reactive protein (mg/dL)	0.06	0.00-0.14
Coagulation		
Prothrombin time international normalized ratio	0.90	
Activated partial thromboplastin time (s)	20.2	24-39
D-dimer (μg/mL)	5.80	0.0-1.0
Arterial gas analysis		
pH	7.29	7.35-7.45
pCO_2 (mm Hg)	38.6	35-45
pO_2 (mm Hg)	73.3	75-110
HCO_2 (mmol/L)	18.8	20.0-26.0
Base excess (mmol/L)	-7.1	-3.0-3.0
Anion gap (mmol/L)	15.1	10-14
Lactate (mmol/L)	5.0	0.5-2.0

Immediately after arrival, the patient required mechanical ventilation, and norepinephrine and vasopressin infusions for respiratory failure, shock, and impaired consciousness. After admission, intensive care treatment including continuous atropine infusion was initiated (**Figure 2**). Although bowel sounds were hyperactive on arrival, they decreased markedly after initiation of atropine therapy. No bowel movement was observed on the day of admission. However, bowel movements resumed on day 2 after manual fecal disimpaction was performed by nursing staff. Serum butyrylcholinesterase activity decreased from 32 U/L on admission to a nadir of 7 U/L on day 2, then gradually increased to 88 U/L by day 10 (**Figure 2**). Subsequently, the patient's hemodynamic status gradually improved. Norepinephrine and vasopressin infusions were discontinued on day 5. Continuous atropine infusion was discontinued on day 6, and mechanical ventilation was discontinued on day 9. Thereafter, the patient's general condition steadily improved. He was eventually discharged on day 77.

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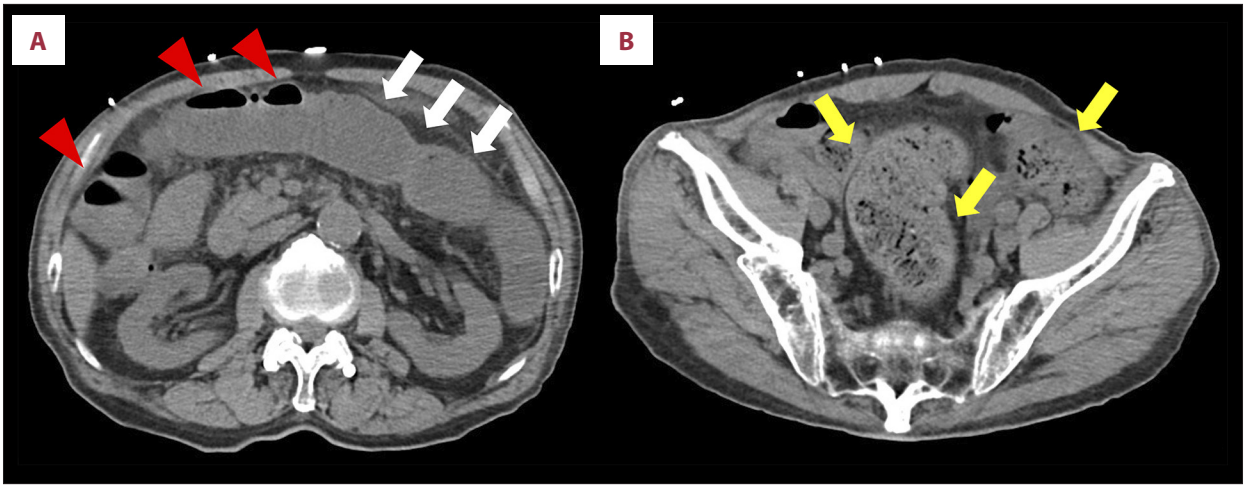


Figure 1. Abdominal computed tomography findings on admission. (**A**) Fluid retention (white arrows) and air-fluid levels (red arrowheads) in the small intestine. (**B**) Fecal retention extending from the descending colon to the rectum (yellow arrows).

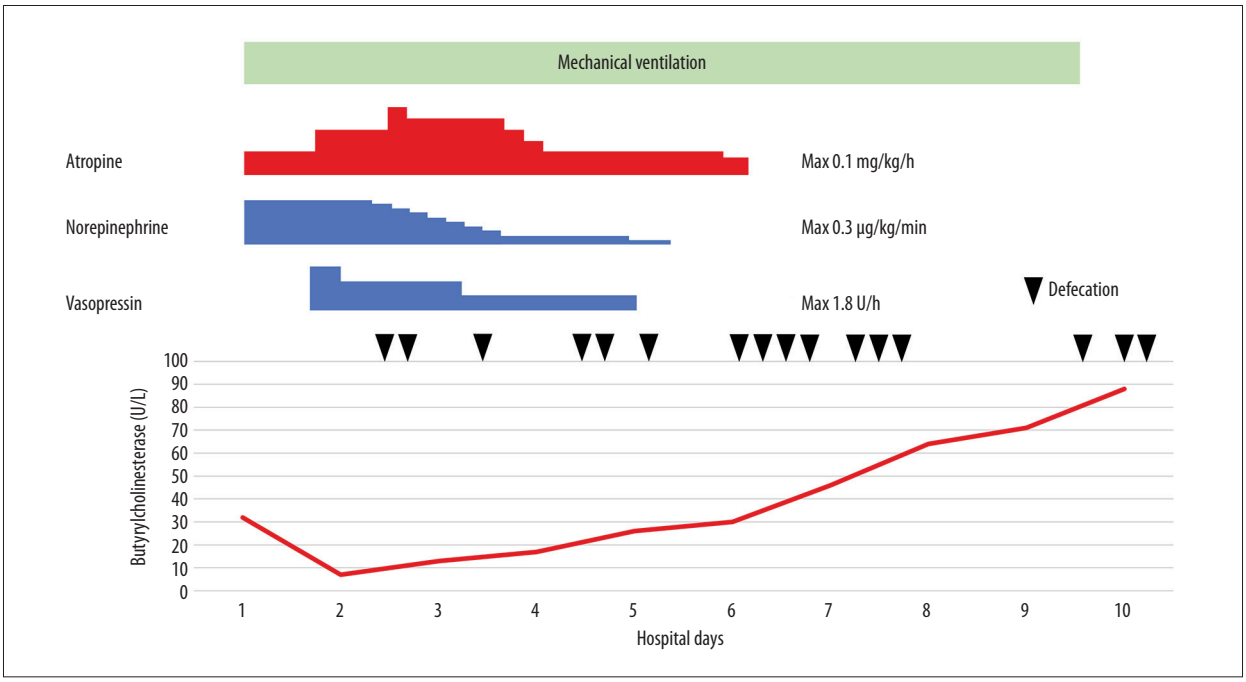


Figure 2. Clinical course during hospitalization. After discontinuation of distigmine and bethanechol and initiation of atropine therapy, serum butyrylcholinesterase activity initially decreased and then gradually recovered. During the acute phase, the patient required mechanical ventilation and continuous infusions of norepinephrine, vasopressin, and atropine. Black inverted triangles indicate episodes of defecation.

Discussion

In the present case, an older adult patient with severe constipation developed life-threatening cholinergic crisis while receiving usual-dose distigmine and bethanechol for neurogenic bladder. He presented with bradycardia, shock, and respiratory failure, requiring intensive care with mechanical ventilation, vasopressors, and continuous atropine infusion. Severe constipation was evident from his long-standing history of poorly controlled constipation and marked fecal retention on abdominal computed tomography.

Previous reports have described cholinergic crisis associated with cholinesterase inhibitors, including distigmine bromide, particularly in older patients and those with renal dysfunction or low body weight [5,6]. In the present case, the advanced

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age and renal dysfunction observed on admission may have increased the patient's susceptibility to cholinergic toxicity. However, the patient tolerated distigmine for 3 months and a combination of distigmine and bethanechol for 1 month without any apparent cholinergic symptoms before the present episode. Therefore, severe constipation was not considered a proven primary cause but rather a possible additional contributor to the development or persistence of cholinergic toxicity in this susceptible patient.

However, the potential role of constipation-related intestinal stasis as a risk factor for cholinergic crisis has not yet been widely recognized. In the present case, the patient received laxatives and probiotics for chronic constipation, but his constipation was poorly controlled at the time of presentation. In addition, high-dose norepinephrine and vasopressin were required for circulatory support until bowel movements resumed on day 2. Afterward, the need for vasopressors and atropine gradually decreased. This temporal association raises the possibility that severe fecal retention may have contributed to the prolonged cholinergic toxicity.

Kobayashi et al [7] reported cases of cholinergic crisis in patients receiving distigmine therapy who developed bowel obstruction. Sera et al [8] reported a cholinergic crisis in a patient receiving distigmine and bethanechol who had severe constipation despite normal renal function shortly before onset. Umeya et al [9] reported a case of cholinergic crisis in a patient with severe constipation who received bethanechol therapy. Distigmine has a reported bioavailability of approximately 4.65%, and most of the orally administered drug is believed to be excreted in feces [10]. Although the pharmacokinetics of bethanechol have not been fully characterized, it is primarily excreted through urine and bile [9]. One possible explanation is that severe constipation-related intestinal stasis may have contributed to prolonged cholinergic toxicity.

Although a causal relationship cannot be established from a single case, the temporal association observed in this patient raises the possibility that severe constipation may have acted as an additional contributor to cholinergic toxicity, alongside previously reported risk factors such as advanced age, renal dysfunction, and low body weight. When combination therapy with cholinesterase inhibitors and cholinergic agonists is required, careful monitoring for cholinergic toxicity may be warranted, particularly in patients with bowel dysfunction and other reported risk factors. Furthermore, because older adults are susceptible to chronic constipation due to decreased colonic motility and impaired rectal sensation, their bowel status should be carefully assessed and monitored.

Conclusions

In this case, a life-threatening cholinergic crisis occurred during standard-dose treatment with distigmine and bethanechol in an older adult patient with severe constipation. Previously reported risk factors for distigmine-associated cholinergic toxicity include advanced age, renal dysfunction, and low body weight. Severe constipation may represent a possible additional contributor to cholinergic toxicity. However, the temporal association observed in this case did not establish causality. Careful assessment of bowel status, together with consideration of previously reported risk factors, may be warranted in patients receiving combined cholinergic therapy.

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Informed Consent

Informed consent was obtained from the patient's legal guardian for publication of this case report.

Institution Where Work Was Done

Miyazaki Prefectural Nobeoka Hospital, Nobeoka, Miyazaki, Japan.

Declaration of Figures' Authenticity

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References:

1. Chang L, Chey WD, Imdad A, et al. American Gastroenterological Association-American College of Gastroenterology clinical practice guideline: Pharmacological management of chronic idiopathic constipation. Gastroenterology. 2023;164(7):1086-106
2. Rowe TA, Juthani-Mehta M. Urinary tract infection in older adults. Aging Health. 2013;9(5):519-28
3. Vinarov Z, Abdallah M, Agundez JAG, et al. Impact of gastrointestinal tract variability on oral drug absorption and pharmacokinetics: An UNGAP review. Eur J Pharm Sci. 2021;162:105812
4. Kim DK. Current pharmacological and surgical treatment of underactive bladder. Investig Clin Urol. 2017;58(Suppl. 2):S90-S98
5. Ohbe H, Jo T, Matsui H, Fushimi K, Yasunaga H. Cholinergic crisis caused by cholinesterase inhibitors: A retrospective nationwide database study. J Med Toxicol. 2018;14(3):237-41

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Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

6. Sobajima Y, Hiramatsu T, Matsuura R, et al. [A case of cholinergic crisis with persistent watery diarrhea.] Nihon Shokakibyo Gakkai Zasshi. 2020;117(4):313-20 [in Japanese]
7. Kobayashi K, Sekiguchi H, Sato N, Hirose Y. [Bowel obstruction-induced cholinergic crisis with progressive respiratory failure following distigmine bromide treatment.] Chudoku Kenkyu. 2016;29(1):26-29 [in Japanese]
8. Sera T, Kusunoki S, Shime N. Unexpected cholinergic crisis caused by distigmine bromide: A case report. Medicine (Baltimore). 2022;101(47):e31677
9. Umeya T, Kumazaki S, Ando K, et al. Cholinergic crisis caused by bethanechol and glycerin enema in a patient with diabetic neuropathy: A case report. J Hosp Gen Med. 2025;7(2):58-60
10. Vree TB, Waitzinger J, Hammermaier A, Radhofer-Welte S. Absolute bioavailability, pharmacokinetics, renal and biliary clearance of distigmine after a single oral dose in comparison to intravenous administration of 14C-distigmine bromide in healthy volunteers. Int J Clin Pharmacol Ther. 1999;37(8):393-403

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