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【 CASE REPORT 】

Cholinergic Crisis Owing to Distigmine Bromide Complicated by Hyperosmolar Hyperglycemic State

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Abstract:
Distigmine bromide is widely used to treat neurogenic bladder and causes cholinergic crisis, a serious side effect. We herein report about a patient with distigmine bromide-induced cholinergic crisis complicated by a hyperosmolar hyperglycemic state (HHS). On admission, the patient was diagnosed with HHS based on the medical history and laboratory test results. However, she also had bradycardia, miosis, and low plasma cholinesterase activity. We later found that she had received distigmine bromide, which led to a diagnosis of cholinergic crisis. We suggest that the exacerbation of pathology, including HHS, can cause cholinergic crisis in patients receiving distigmine bromide.

Key words: distigmine bromide, cholinergic crisis, hyperosmolar hyperglycemic state, bradycardia, miosis, low plasma cholinesterase activity

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Introduction

Distigmine bromide is classified as a cholinesterase inhibitor and is used for the treatment of underactive neurogenic bladder. In older adults, detrusor contractility, urine flow, and bladder sensation are significantly reduced. Long-term administration of distigmine bromide is required to treat these neurogenic bladder symptoms (1, 2). However, inadvertent administration of distigmine bromide may result in cholinergic crisis with an excess of acetylcholine (3). The frequency of cholinergic crises is rare (4); however, symptoms include diarrhea, bradycardia, miosis, and sweating.

We herein report a patient who received long-term distigmine bromide treatment and developed dehydration and renal dysfunction owing to a hyperosmolar hyperglycemic state (HHS) that led to cholinergic crisis.

Case Report

An 87-year-old woman who was living in a group home presented to our emergency department with unconsciousness. Her activities of daily living required full assistance, and her food intake had been gradually decreasing for the preceding few days; however, her condition worsened after lunch on the day of admission. She had a history of type 2 diabetes, hypertension, dementia, neurogenic bladder, cataract, angina, Meniere's disease, disc herniation, and colorectal cancer. Any use of prescription drugs was unknown upon admission.

Her body weight and body mass index were 38.5 kg and 17.3, respectively. Her initial vital signs were as follows: respiratory rate: 18 breaths/min, blood pressure: 102/49 mm Hg, heart rate: 57 beats/min, temperature: 36.9℃, peripheral capillary oxygen saturation: 92% with oxygen delivered through a face mask (6 L/min), and Glasgow Coma Scale score of E2V1M6 upon admission. The patient's pupil diameter was less than 1 mm, and miosis was recognized (Table 1). Laboratory test results are shown in Table 2. As the patient had hyperglycemia owing to a history of type 2 diabetes but no evidence of acidosis and a low urinary ketone level (1+), a diagnosis of HHS was confirmed. A neurological examination and brain computed tomography were performed to identify HHS complications; however, no cerebral

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edema was noted. Based on the above results, the patient received 1 L of normal saline intravenously in the emergency department and subsequently an additional 1 L of normal saline in the intensive-care unit. To treat HHS, she was administered a continuous regular insulin dose of 0.5 units/h. The insulin dose was adjusted according to the fluctuation in the blood glucose level (Figure). Laboratory examinations were performed every three hours to assess and modulate electrolyte changes.

A few hours after her admission, we discovered that the patient had been taking distigmine bromide for three years. Since she presented symptoms of miosis, bradycardia, and hypercapnic respiratory failure and had low cholinesterase levels on biochemical tests, she was suspected of being in distigmine bromide-induced cholinergic crisis complicated by HHS. To treat the bradycardia associated with cholinergic crisis, atropine sulfate 0.5 mg was intravenously administered. To maintain a heart rate of ≥40 beats/min, atropine sulfate 0.5 mg/h was continuously infused. When it was possible to maintain a constant heart rate, atropine sulfate was discontinued (total administration period: 1.5 days).

A few days later, her symptoms, including miosis, bradycardia, and hypercapnic respiratory failure, were nearly resolved with a concomitant increase in serum cholinesterase levels. At the same time, an improvement in her awareness level was observed. The insulin therapy was adjusted to subcutaneous insulin injection. Finally, she received insulin lispro (14 units before breakfast, 7 units before lunch and dinner) and insulin glargine U-300 (8 units before breakfast).

On day 19 after admission, her serum cholinesterase levels returned to baseline at 151 IU/L. The blood distigmine bromide level was 43.8 ng/mL upon admission and gradually decreased with treatment progression. Consequently, a diagnosis of distigmine bromide-induced cholinergic crisis was confirmed. On day 23, she was transferred to the medical office.

Table 1. Transition of Pupil Diameter.

Day	Time	Pupil diameter [mm/mm]	
0	15:30	1.0/1.0	←Start of atropine administration
0	22:00	1.0/1.0	
1	9:00	2.0/2.0	
1	14:00	1.5/1.5	
1	21:00	2.0/2.0	
2	7:00	2.5/2.5	←End of atropine administration
2	14:00	2.5/2.5	
2	19:00	2.5/2.5	
3	9:00	2.5/2.5	
3	14:00	2.5/2.5	
3	21:00	2.5/2.5	
4	9:00	2.5/2.5	
4	14:00	3.0/3.0	
4	21:00	3.0/3.0	

Table 2. Laboratory Data at the Time of Admission.

Arterial blood gas		Blood chemistry	
pH	7.31	Glucose	998 mg/dL
pCO_2	49.4 mm Hg	HbA1c	11.5 %
pO_2	73.2 mm Hg	C-peptide	1.61 ng/mL
HCO_{3-}	24.4 mmol/L	Serum osmolarity	414 Osm/kg H_2O
BE	-1.7 mmol/L	Total protein	5.7 g/dL
Lactate	2.4 mmol L	Albumin	3.1 g/dL
		BUN	72 mg/dL
Peripheral blood		Creatinine	1.38 mg/dL
WBC	8,100 /μL	eGFR	28.0 mL/min
RBC	$390\times10_4$ /μL	AST	13 IU/L
Hb	14.5 g/dL	ALT	11 IU/L
PLT	$7.60\times10_4$ /μL	Cholinesterase	26 IU/L
		γ-GTP	16 IU/L
		CK	92 IU/L
		Na	165 mEq/L
		K	3.0 mEq/L
		Cl	115 mEq/L
		CRP	4.10 mg/dL

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BUN: blood urea nitrogen, BE: base excess, CK: creatine kinase, Cl: serum chloride, CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, Hb: hemoglobin, HbA1c: hemoglobin A1c, HCO_{3-}: bicarbonate, K: serum potassium, Na: serum sodium, pCO_2 : partial pressure of carbon dioxide, PLT: platelet count, pO_2: partial pressure of oxygen, RBC: red blood cell count, WBC: white blood cell count, γ-GTP: γ-glutamyl transpeptidase

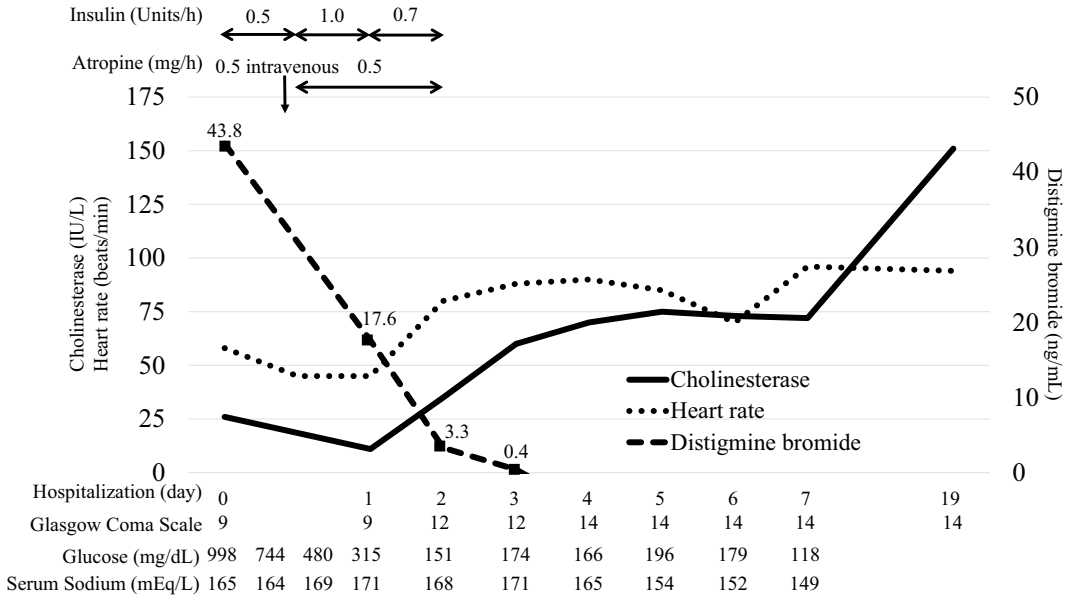

Figure. **Patient's clinical course during hospitalization. Atropine 0.5 mg was intravenously administered on the day of hospitalization (arrow) and 0.5 mg/h was continuously infused.**

Discussion

Distigmine bromide is a cholinesterase inhibitor used for urge incontinence associated with neurogenic bladder. This drug is also known to cause cholinergic crisis, a rare but serious adverse reaction (5). Distigmine bromide-induced cholinergic crisis occurs most often at the beginning of administration (6, 7). While some reports have indicated that cholinergic crisis can occur during long-term administration of distigmine bromide (8, 9), no studies have reported distigmine bromide-induced cholinergic crisis complicated by HHS.

Distigmine bromide is water-soluble and takes effect one to two hours after administration. Since this drug continuously binds to acetylcholinesterase, it has a long duration of action (half-life of 72 hours), and it takes approximately one week for all of its actions to disappear (10). The drug is mainly excreted by the kidneys, which can cause blood levels of distigmine bromide to increase in patients with an impaired renal function. In our case report, the blood level of distigmine bromide increased to 43.8 ng/mL compared to the therapeutic range of 5-10 ng/mL (11). We suspect that the cause of the increased blood concentration of distigmine bromide was dehydration owing to a complication of HHS that reduced the renal function and prolonged the excretion of the drug.

In Japan, the usual dose of distigmine bromide previously ranged from 5 mg/day to 20 mg/day. However, owing to the high incidence of cholinergic crisis (6, 9, 11), the dose of distigmine bromide for dysuria was limited to 5 mg/day as of March 2010. As a result, studies of cholinergic crisis owing to distigmine bromide are decreasing. Nevertheless, long-term administration of distigmine bromide (5 mg/day) may cause cholinergic crisis (12, 13); thus, the occurrence of cholinergic crisis should be considered, regardless of the dose of distigmine bromide.

As in this case, older adults with a poor general condition are more likely to experience cholinergic crisis owing to long-term administration of distigmine bromide than younger ones (14). Risk factors for cholinergic crisis include an increased age, low weight, renal dysfunction, dehydration, liver dysfunction, and malnutrition (15, 16). This case involved a high-risk patient with cholinergic crisis, as the patient was older and had a low weight, renal dysfunction, dehydration, and malnutrition. However, even in relatively young patients, there are some studies in which cholinergic crisis was caused by the deterioration of the health condition (11, 12). All patients who are treated with distigmine bromide should be aware of the possibility that cholinergic crisis may be caused by an increase in the blood levels of distigmine bromide (17).

Cholinergic crisis is a clinical condition that results from the overstimulation of nicotinic and muscarinic receptors at neuromuscular junctions and synapses following the administration of cholinesterase inhibitors (18). It usually results from the inactivation or inhibition of acetylcholinesterase, which is the enzyme involved in the breakdown of acetylcholine. The excessive accumulation of acetylcholine at neuromuscular junctions and synapses causes symptoms of muscarinic and nicotine toxicities, including diarrhea, miosis, and bradycardia (18). In our case, no characteristic diarrhea was observed early at the onset of cholinergic crisis. Previous studies have reported that approximately half of the patients with distigmine bromide-induced cholinergic crisis presented with gastrointestinal symptoms, including diarrhea (6). Based on these results, a diagnosis of cholinergic crisis requires the presence of multiple symptoms rather than

a single symptom because approximately half of patients do not experience diarrhea.

In recent years, several reports have identified risk factors for prevention and early detection of the onset of distigmine bromide-induced cholinergic crisis (19, 20). Since distigmine bromide is a drug that needs to be taken for a long period of time, it is presumed that such regular monitoring will be necessary in the future.

Conclusions

We encountered a case of cholinergic crisis owing to distigmine bromide along with HHS. Regardless of the patient's age or the dose and duration of distigmine bromide administration, it should be noted that cholinergic crisis owing to distigmine bromide can occur when a patient's condition worsens or begins to deteriorate.

The authors state that they have no Conflict of Interest (COI).

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