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Anticholinergic symptoms in a patient with a bupropion overdose successfully managed with physostigmine: a case report

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Abstract : We report the case of anticholinergic poisoning in a patient suffering from an overdose of bupropion. The patient presented with bilateral mydriasis, involuntary movements and signs of agitation. Bupropion is commonly used as antidepressant and smoking cessation aid. It inhibits neuronal reuptake of dopamine and norepinephrine and also antagonizes acetylcholine at the level of the nicotinic receptor sites. So far bupropion overdose resulting in symptoms mimicking an anticholinergic syndrome has rarely been reported in literature.
In this case, one milligram of intravenous physostigmine, an acetylcholinesterase inhibitor, rapidly resolved patient agitation and mydriasis. This case indicates that physostigmine might be used as an antidote to quickly reverse the central and peripheral anticholinergic symptoms in patients with an overdose of bupropion.

Key words : anticholinergic symptoms ; bupropion overdose ; physostigmine.

Bupropion hydrochloride is an atypical antidepressant, also used as a smoking cessation aid. It is an antagonist of the nicotinic receptors of the autonomic ganglia and the central nervous system (1). Current management of bupropion overdose is mainly supportive ; no specific antidote is available. Physostigmine is a short-acting acetylcholinesterase inhibitor that can pass freely into the central nervous system (CNS) and reverse both central and peripheral anticholinergic effects (2).

Case Report

A 58-year old woman was admitted to the Intensive Care Unit (ICU) from the emergency department. The initial prehospital assessment revealed hypoxia (SpO_2 of 60% without supplemental oxygen), unconsciousness (Glasgow Coma Scale (GCS) 3/15) and mydriatic and non-reactive to light pupils. Following rapid sequence intravenous (IV) induction with 100mg rocuronium, 100µg fentanyl and 200mg ketamine, the trachea was intubated and ventilation was initiated. Because she was found alone at home, no further information was available.

On admission, blood pressure was 141/74 mmHg, heart rate 74/min, body temperature 31.2°C, glucose level 89mg/dl. Pulse oximetry during PRVC-ventilation with 100% FiO_2 was 100%. Brain-CT scan was normal. Chest-CT scan showed a pneumonic infiltrate. Lab results showed : hemoglobin 11.8g/dl (normal range 12-16g/dl), C-reactive protein 6.75mg/l (normal range 0-10 mg/dl) and white blood count 9.6. 10^3 mm^{-3}(normal range 4-10 10^3 mm^{-3}). The serum creatinine level of 1.8 mg/dl (normal range 0.7-1.3 mg/dl) suggested an acute kidney injury. Electrolytes were normal. Carbon monoxide was 0.1%. Ethanol- and paracetamol levels were low. Other toxicological screening were ongoing. The first arterial blood gas analysis (while intubated and ventilated) showed a combined metabolic and respiratory acidosis with a pH of 7.25 (normal pH 7.38-7.44), a $PaCO_2$ of 50mmHg (normal range 35-45 mmHg), a PaO_2 of 127mmHg (normal range 80-100 mmHg), lactate at 17mg/dl (normal range 6-16 mg/dl), HCO_3^- at 22mmol/l (normal range 23-28 mmol/l) and a base excess of - 5.6 mEq/l (normal range –2 - +2 mEq/l).

The initial therapy for hypothermia was the administration of 500ml of warm fluid and the use of an external heating with a forced-air

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patient warming device. Hypotension was treated with norepinephrine (0.15µg/kg/min). Empirical antibiotic therapy (amoxicillin-clavulanic acid with clarithromycin) was given for the pulmonary infection. The patient was transferred to the ICU with a probable diagnosis of septic shock and encephalopathy based on a pulmonary infection. A central nervous system infection or intoxication could not be excluded.

On ICU admission, the body temperature was still 31.2°C despite external warming. GCS was still at 3/15. Residual neuromuscular blockade was suspected despite a 180-minute delay after administration of rocuronium. Complete recovery of motor response was achieved quickly after administration of sugammadex. This prolonged effect can be mainly attributed to hypothermia (3). However, the patient was very agitated and had non-reactive mydriasis. As prolonged ventilation was required due to hypoxia, sedation with propofol and remifentanil was initiated.

Thirty-six hours after admission, involuntary movements persisted, and the pupils remained dilated and unresponsive to light. Epileptic activity was excluded by EEG.

We were then informed of her usual medication consisting of bupropion 150mg 1dd, ezetimide 10mg 1dd, amlodipine 10mg 1dd, levothyroxin 50µg 1dd and alprazolam 0.25mg if needed. We also learned that she had formulated suicidal tendencies to a friend. The level of bupropion in the blood sample taken on admission to the hospital was found to be very high with a value of 1077 ng / ml (therapeutic level <100 ng / ml).The level of the active metabolite hydroxybupropion was 6932 ng/ml (therapeutic level <1500 ng/ml). Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and excreted by the kidneys. The elimination half-life of 20-30 hours can take up to 60 hours, or longer in case of renal impairment (4). Other tested molecules were absent or within therapeutic range (table 1).

Forty-two hours after admission, the patient was still unconscious with non-purposeful movements. The exact etiology of her condition was unclear, but there was no evidence of intracranial pathology, and she had been exposed to several neuroactive substances. The main alternative causes of coma having been excluded, a test dose of 1 mg of physostigmine was administered based on the personal experience of the treating clinician. Physostigmine had previously given positive results in comparable clinical cases. Physostigmine is a short-acting acetylcholinesterase inhibitor, described to reverse delirium from acute antimuscarinic toxicity through increasing synaptic acetylcholine (2). Within 10-15 minutes after administration, the patient woke up, was adequate, and no longer agitated. She was extubated. Pupils returned to normal.

Table 1.

Blood level and therapeutic range of tested drugs at the moment of hospital admission

Agent	Level (ng/ml)	Therapeutic range (ng/ml)
Bupropion	1077	10-100
Hydroxybupropion	6932	850-1500
Diazepam	3.8	125-250
Desmethyl diazepam	25.8	200-800
Alprazolam	31	10-80
Tricyclic antidepressants*	negative	
Duloxetine	57	30-120

* Tricyclic antidepressants screened were amitriptyline, clomipramine, desipramine, doxepine, dosulepine, imipramine, nortriptyline, protriptyline, trimipramine.

The next day, she remained adequate.She was able to tell her story and confirmed the intentional overdose. None of the described adverse side effects of physostigmine, such as bradycardia, seizures, or respiratory distress, were observed (5).

After three more days to recover from the pneumonia, the patient was transferred to the ward. The neurological recovery was uneventful. The patient did not report any explicit reminder of the period of agitation and confusion.

Discussion

This case demonstrates that physostigmine, conventionally used to treat overdose of muscarinic agonists, was very effective in reversing the symptoms of bupropion overdose.

However, in this case, many symptoms typical of bupropion overdose (6) were absent during the observation period. This may be because the patient was already sedated and intubated at the time of hospitalization.

The clinical anticholinergic symptoms are mostly described with tricyclic antidepressants, antipsychotics and antihistamines (7). It is a manifestation of competitive antagonism of acetylcholine at peripheral and central muscarinic receptors (8). The peripheral anticholinergic symptoms include dry mouth, blurred vision and photophobia, due to dilated pupils. The skin may be warm and dry, and patients may present a paralytic ileus and urinary retention. The central anticholinergic overactivity most commonly shows agitation that may progress

to a hyperactive (agitated) delirium, often with incoherent speech, and hallucinations.

Bupropion, however, is considered to have, for all practical purposes, no antimuscarinic activity (9). As such, the clinically observed – both central and peripheral – anticholinergic symptoms must have resulted from its antinicotinic effects. Bupropion interferes with the ganglion-type and CNS-type nicotinic receptors (10).

In this case, we predominantly observed mydriasis and hyperactive agitation as anti-cholinergic symptoms. In addition, the symptoms were most probably not provoked by interaction with muscarinic receptors. It is therefore remarkable that although there was no actual anticholinergic syndrome, there was a dramatic improvement after the administration of 1mg physostigmine through antagonism of nicotinic receptors.

There is no known specific antidote for bupropion overdose. Management of bupropion overdose is mainly supportive. In one case report of a mixed overdose of bupropion and diphenhydramine (a H_1-antihistaminicum with anticholinergic activity), physostigmine also successfully resolved the hallucinations and antimuscarinic symptoms.

Unexpectedly, we noticed a reversal in our patient's clinical presentation with a single 1mg dose of physostigmine.

Physostigmine has a half-life of 1 to 2 hours, or even shorter, while bupropion and its metabolites can take up to 60 hours. Repeated administration would therefore be necessary (11, 12).

This impressive difference in the half-life of physostigmine versus the course of symptoms reversal over time indicates that the beneficial effect of physostigmine cannot be attributed purely to an isolated pharmacological antagonist effect of bupropion at the level of the acetylcholine receptor. Nevertheless, this single dose was clearly sufficient to reverse the symptoms. Based on our observations, we can only speculate on the mechanism of this lasting reversal. However, a retrospective analysis of comparable cases also described that a minority of cases (12%) did not relapse after an initial dose of physostigmine for the treatment of anticholinergic poisoning (the mean initial dose was 2.2mg) ; only 58% of patients received multiple doses or continuous infusion (13). It appears that in these cases, as well as in our case, an aberrant feedback mechanism in the brain was interrupted by physostigmine, leading to lasting benefits.

The ability of bupropion to interact with specific nicotine receptor subtypes has been studied using various cell expression systems. Inhibition of these nicotine receptor subtypes by bupropion is not overcome by increased agonist concentrations, indicative of a non-competitive mechanism of action (14). In addition, physostigmine is an acetylcholinesterase inhibitor classically administered for muscarinergic intoxication. Although in this patient, there was nicotine agonist poisoning, the symptoms were typically muscaric. Despite bupropion lacks direct antimuscarinic affinity and exhibits a uncompetitive antagonism, the observation that increased acetylcholine levels resolve anticholinergic symptoms indicates that the mechanism of action of physostigmine must be more complex than the effects on a single receptor.

It is known that bupropion rarely exhibits anticholinergic effects, except when combined with other psychoactive drugs (15). The observed clinical effect of physostigmine is therefore probably explained by the cessation of the delirium caused by overdose of bupropion. Despite the clear and rapid resolution of clinical symptoms, the exact mechanism by which physostigmine reversed the symptoms remains to be elucidated. Furthermore, it is interesting to wonder about the effect that physostigmine would have had on the evolution of symptoms if it had been administered (much) earlier.

It is important to note that ketamine, which is thought to bind to muscarinic and nicotinic acetylcholine receptors, has been used for the induction of anesthesia. Anticholinergic symptoms after administration of ketamine are described (16) and could be successfully antagonized with physostigmine (17). Although ketamine is a short-acting drug, an influence of ketamine on the long-lasting anticholinergic state of the patient by a strengthening effect on the anticholinergic action of bupropion cannot be excluded.

Likewise, fentanyl is reported to induce serotoninergic toxicity in rare cases, althought it is widely used. These cases are, however, always associated with much higher (often maintenance) doses of fentanyl and in the context of polypharmacy with other serotonergic agents, such as SSRIs (18). While the contribution of fentanyl, if any, is probably low, we cannot exclude that fentanyl is a contributing factor in the symptoms observed.

The significantly increased levels of bupropion and hydroxybupropion, in the absence of markedly increased levels of other drugs tested, suggest a strong likelihood that symptoms at the time of admission were primarily due to isolated bupropion intoxication. Other drugs not detected may have been involved in this poisoning. Therefore, it may

be premature to assert a cause and effect relationship based on this single case. Second, caution is advised when administering physostigmine to treat bupropion overdose, as there is often no peripheral anticholinergic effects to counter potential cholinergic agonist effects.

Conclusion

We report an unusual case of bupropion poisoning in which therapy consisting of the administration of physostigmine to reverse the effects of bupropion at the central nicotinic receptors and possibly muscarinic receptors was successful. This case strongly indicates that 1mg of physostigmine, a cholinesterase inhibitor,resulted in a complete reversal of the anticholinergic symptoms within 10-15 minutes.

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