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RESEARCH ARTICLE

A CASE OF MIXED SSRI AND BETA BLOCKER TOXICITY

[1,*]Dr. Kishore Kumar Aindala and [2]Dr. Indranil Das

[1]Emergency Resident (PGY 2), Institute of Emergency Medicine, Medeor Hospital, IMT Manesar, Gurgaon Haryana
[2]Consultant, Institute of Emergency Medicine, Medeor Hospital, IMT Manesar, Gurgaon Haryana

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**Corresponding author:*
Dr. Kishore Kumar Aindala

ABSTRACT

The B-adrenergic receptor antagonists, or B-blockers, are common medications used in the treatment of various cardiovascular, neurologic, endocrine, ophthalmologic, and psychiatric disorders. Because of their widespread availability, accidental and intentional toxicity is common. Also SSRI are present in the prescriptions of Neurologists and psychiatrists. The Emergency physicians also encounter many of the overdose of these drugs in patients who are on poly-pharmacy along with accidental and intentional ingestion. In our present case we will be describing a case of this mixed toxicity/overdose in a 30year old male patient who presented to the Emergency.

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INTRODUCTION

In 2008, the American Association of Poison Control Centers received reports of 21,282 exposures to B-blockers with six associated deaths. Less common uses include prophylactic treatment of migraine headaches and treatment of arterial vasospasm due to Raynaud disease, esophageal spasm, and pulmonary hypertension. Among all the exposures to cardiovascular agents, B-blocker exposures were the leading cause of poison center calls and ranked among the top three in this class as a cause of severe toxicity and mortality. The B-adrenergic receptors are membrane glycoproteins present in various tissues. At least three B-adrenergic receptor subtypes have been characterized (B1, B2, B3). These receptors play a critical role in cardiovascular physiology by modulating cardiac activity and vascular tone. During times of stress (i.e., catecholamine release), B-adrenergic receptor stimulation increases myocardial and vascular smooth muscle cell activity through a sequence of intracellular events.Cardiac myocyte B-receptor and calcium signaling is the major activity. Calcium plays a key role in intracellular signaling and myocyte contraction. Binding of a B-agonist to the B_1-adrenergic receptor (B1) on the cell surface activates the Gs protein. The Gs protein then activates adenylate cyclace (AC), which converts adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP).

The increased cAMP activates protein kinase A (PKA). Activated PKA causes the L-type voltage-dependent calcium channel (L-VDCC) to open. Extracellular calcium (Ca^{2+}) then enters the cell and binds to the ryanodine receptor (RyR) in the sarcoplasmic reticulum, causing an efflux of sequestered Ca^{2+} out of the sarcoplasmic reticulum into the cell. The released Ca^{2+} binds to troponin, which allows the myosin and actin interaction that causes contraction of the cardiac myocyte. Glucagon is a stress-reactive protein that independently activates adenylate cyclase. cAMP is metabolized by phosphodiesterase (PDE) into inactive adenosine 5'-monophosphate (5'AMP).The B-blockers modulate the activity of myocyte and vascular smooth muscle contraction by decreasing calcium entry into the cell. Therapeutically, B-blockade lessens the work performed by the diseased or injured myocardium. On the other hand, excessive B-blockade may lead to profound pump failure, with bradycardia, decreased contractility, and hypotension. The pharmacologic properties of various B-blockers influence their spectrum of action, adverse drug reactions, and toxicity. These properties include receptor selectivity, sodium channel blockade (also known as *membrane-stabilizing activity*), lipid solubility, protein binding, and partial agonist activity . For example, highly lipid-soluble agents, such as propranolol, readily cross the blood–brain barrier and achieve high concentrations in brain tissue.

This may contribute to the more severe central nervous system manifestations of mental status depression, seizures, and coma seen after an overdose of such agents. Several B-blockers inhibit myocardial sodium channels, similar to quinidine and cyclic antidepressants, which renders these drugs potentially more cardio depressant following overdose. However, in massive overdoses, probably all B-blockers can produce severe cardio depressant effects. Propranolol is the most common beta-blocker involved in severe beta-blocker poisoning. It is nonselective and has membrane-stabilizing effects that are responsible for CNS depression, seizures, and prolongation of the QRS complex. Beta-blockers have been in use for nearly 50 years. In addition to their traditional role in treating hypertension and other cardiovascular disorders, beta-blockers are also used for additional purposes such as migraine headaches, hyperthyroidism, glaucoma, anxiety, and various other disorders. As a result of their expanded use, the incidence of overdose with these agents has also increased. Beta-blocker toxicity in children usually results from exposure to an adult's unattended medications. Beta-blocker toxicity in adults usually results from a suicide attempt or an accidental overdose of a routine medication. A review of US poison center data for 2004 showed over 48,000 exposures to selective serotonin reuptake inhibitors (SSRIs).SSRIs represent a group of chemically diverse agents that share the ability to inhibit the presynaptic uptake of serotonin within the central nervous system. They are commonly prescribed for the initial treatment of mild to moderate depression, generalized anxiety disorder, and obsessive-compulsive disorder and are widely used for other diseases of neurologic origin including neuropathic pain (4–6 Miller TR, Lestina DC. Costs of poisoning in the United States and savings from poison control centers: a benefit-cost analysis. Ann Emerg Med 1997; 29: 239–245,Poisindex system, RK Klasco. Thomson Micromedex, Greenwood Village, CO 2004). Due to their less troublesome side effect and safety profiles, the SSRIs have essentially replaced the tricyclic antidepressants as first-line therapy for depression. Antidepressant overdoses are among the most common prescription drug overdoses managed by poison centers.

This is in part because of their high prevalence of therapeutic use but also because of their use by patients at high risk for intentional ingestion. According to the Toxic Exposure Surveillance System (TESS) of the American Association of Poison Control Centers, there were 48,204 human ingestions of selective serotonin reuptake inhibitor antidepressants (SSRIs) reported to poison centers in the US in 2004; 31,181 (65%) were evaluated in healthcare facilities. Children less than 6 years of age accounted for 8,187 (17%) of all reported SSRI ingestions. Major effects occurred in 1,426 SSRI ingestions and 103 ingestions resulted in death; there were known co-ingest ants in all but three deaths. Between 2000 and 2005, there were 44,545 ingestions of SSRIs in children less than 6 years of age reported to TESS. Major effects were noted in 59 cases (0.1%) and there was one reported death. Another complications seen is Serotonin syndrome. Serotonin syndrome occurs when you take medications that cause high levels of the chemical serotonin to accumulate in your body. Serotonin syndrome can occur when you increase the dose of such a drug or add a new drug to your regimen. Certain illegal drugs and dietary supplements also are associated with serotonin syndrome. Serotonin is a chemical your body produces that's needed for your nerve cells and brain to function. But too much serotonin causes symptoms that can range from mild (shivering and diarrhea) to severe (muscle rigidity, fever and seizures). Severe serotonin syndrome can be fatal if not treated. Milder forms of serotonin syndrome may go away within a day of stopping the medications that cause symptoms and, sometimes, taking drugs that block serotonin.

Sign and Symptoms of SSRI overdose

- Seizures
- Arrhythmia
- Rhabdomyolysis
- Disseminated intravascular coagulation
- Acute renal failure
- Respiratory failure

Sign and Symptoms of B-blocker overdose

Cardiac

- Hypotension
- Bradycardia
- Conduction delays and blocks
- Ventricular dysrhythmias
- Asystole
- Decreased contractility

Central nervous system

- Depressed mental status
- Coma
- Psychosis
- Seizures

Pulmonary

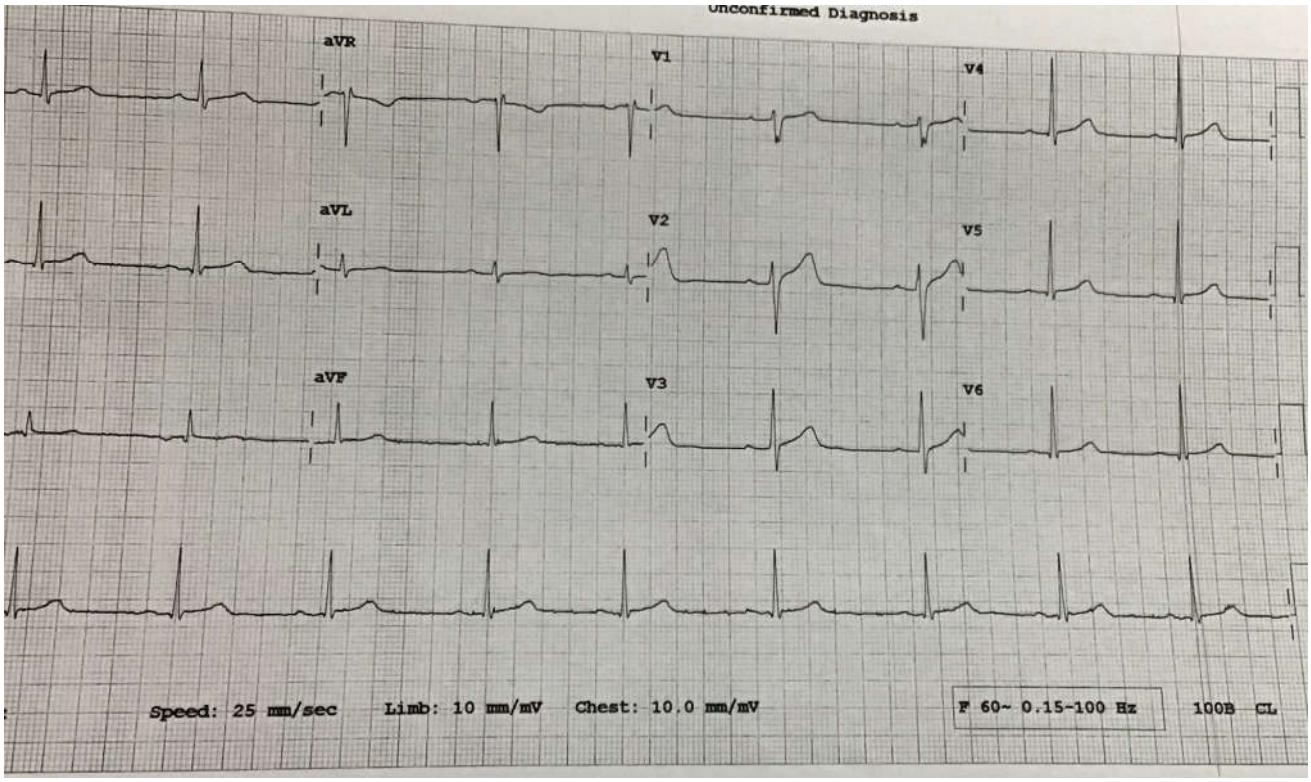
Bronchospasm

Case History: 30yr old male patient was rolled down to Emergency at 7:30 PM with altered mental status and drowsiness. He is a known case of Depressionand has been under treatment withantidepressants. He has become drowsy about 1 hr. 30 min prior to arrival. No h/o any convulsion, no h/o any trauma. As per the accompanying person and the family the patient was started on some medications(probably Propranolol and Escitalopram) by some Physician (prescription not available) 1 week ago. The family gave the history that he had purchased a month supply of medications and since last 3 days as he was upset for some family issues. In the morning he felt mild palpitations and took 20 tablets of Propranolol 40mg and 20 tablets of escitalopram 4 hrs. prior to arrival. In the evening by 6:30PM he started feeling dizziness and then became drowsy and was brought to ED at 7:30 PM. Late in the evening he was not feeling comfortable and hence he was taken to some local physician and in the clinic the physician examined him and referred to higher center. As per the family there was no episode of any convulsion and no bowel or bladder incontinence. In the ED the patient was immediately taken to the monitored bed and hooked to the monitor.

Vitals

Pulse-54/m and regular and no ectopy
BP-90/60mmhg
RR-22/m
Spo2-88% in room air
Temp.- Afebrile
RBS- 82 mg/dl

A 12 lead ECG taken as under



Primary Survey

- Airway- Patent and maintainable
- Breathing- Spontaneously, Spo2-100% with 4 L/m O2 by Nasal Cannula.
- Circulation- Sweating present, BP- 90/60mmhg and CRT-wnl
- Disability- Drowsy but arousable and Obeying Commands and Moving 4 limbs. No FND.
- Env/Exp- Sweating.
- S- Dizziness.
- A – No allergy to drug or food
- M- Propranolol 40mg od and Escitalopram 10mg HS
- P- Depression and Anxiety
- L- 4-5 hrs. ago some snacks
- E- Dizziness.

Secondary Survey

- HEENT- wnl and no JVD and no Carotid bruit
- Chest- B/L vbs and no crepts.
- CVS- s1 s2 and no added sound
- CNS- Pt. drowsy but arousal and no FND
- P/A- soft and no organomegaly and no Guarding and no rigidity, Bowel sounds+
- Extremeties- WNL and only cold and clammy and feeble peripheral pulses and no rash and no injury.

Management in ED: Airway- Maintainable and the pt. put in a Supine position. Breathing- O2 by nasal cannula @ 4l/m Inj. Atropine 0.5mg iv stat. Circulation- Two large bore IV access taken and iv fluid started with Normal Saline Bolus. IV stat.

Inj. Atropine 0.5mg iv stat
Inj. Pan 40mg iv stat
Inj. Metoclopramide 5mg iv stat

Sinus Bradycardia

Echo done in ED showed no RWMA with an EF of 55%. The patient was kept under observation in the ICU under Internal Medicine and Cardiology. The patient was discharged on 3rd day with the advised to follow up in Psychiatry and Int. Medicine OPD.

DISCUSSION

Mixed toxicity with SSRI and B-blocker are not very common. But this patient developed symptoms of both the SSRI and B-blocker overdose. The patient was managed conservatively and as per the unstable Bradycardia algorithm of AHA and the patient recovered.

ED Perspective: ABC and recognition of theToxidrome is a very important in the suspected case of mix drug overdose.

Other Treatment Options

Though Glucagon is a good option in the management, but should be reserved for severe toxicity not responding to routine symptomatic management. High dose insulin and Euglycemia is also a treatment modality for B-blocker overdose. Activated Charcoal is only useful if the h/o oral ingestion within last 1 hr. of presentation. Temporary Pacemaker still remains the final treatment modality for all the unresponsive case of Bradycardia.

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