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Severe beta-blocker overdose in a 65-year-old female

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Introduction: Population of people over 65 years old is one of the groups of the greatest risk of suicide attempt. In this age range the highest suicide rate that results in death is observed. Metabolism alterations and co-morbidities development with age may play major role in increasing suicide rate. Accidental and intentional drug over-ingestions are more common for people with numerous prescriptions and comorbid conditions. Overdose in such patients can pose great threat to patients life.

Aim of the study: The purpose of this study is to depict course of β-adrenolitics and benzodiazpines poisoning on the base of case report.

Materials and methods: The analysis of the patient's medical history and the review of available literature in the PubMed and Google Scholar databases.

Results: The 65-year-old female, was brought by emergency medical services to the Toxicology Clinic due severe drug poisoning. Upon admission patient was unconscious, intubated, on ventilator, in overall severe condition. She presented symptoms of circulatory insufficiency. History revealed overdose of β-adrenolitics and benzodiazepines. The application of proper pharmacological treatment and heart pacing resulted in gradual improvement of patients condition. After one-week stay she was discharged home in good condition.

Conclusions: Course of β-adrenolitics poisoning with addition of benzodiazepines poses great threat, especially when one suffers from numerous comorbidities. Therefore, due to wider availability of drugs and rising number of suicide attempts, as well as events of medication errors, it is crucial to be aware of elder people problems and prevent such situations.

Key words: Betaadrenolitic; betablocker; bisoprolol; estazolam; overdose;

INTRODUCTION

β-adrenolitics (beta blockers,BB) are drugs that cover large part of cardiological drugs prescriptions. Their role is significant in the treatment of heart failure, hypertension, tachydysrhythmias and angina pectoris. They are invaluable medications in treatment of ischemic heart diseases. Moreover, they have been proven to be useful in numerous noncardiologic disorders, like migraine headache, tremor, hyperthyroidism or anxiety. Despite the fact that overdoses of β-blockers are relatively rare, they are associated with significant morbidity and mortality. Poisoning may occur in children as exploratory overingestion, as suicide attempt or as a result of

metabolism alterations. Case of such poisoning may happen even in casual physician practice, as incorrect prescription mixed with metabolizer genes mutations [1].

Beta blockers together with calcium channel blockers are cause of over 65% of deaths from all cardiovascular medications [2]. Patients with underlying medical illnesses, especially with cardiac diseases or numerous comorbidities are at increased risk of poor outcome.

Beta blockers are divided into two main groups: non-selective and selective, depending on the receptor specificity. Beta blockers reduce effects of catecholamines on the cardiac tissue via competitive antagonizing β-1 adrenoceptors in myocardium. This causes decrease in adenyl cyclase function, reduction of cyclic AMP (cAMP) production and phosphorylation and inhibition of opening of L-type calcium channels. As a result, via blockade of second messager system, calcium entry to cardiomyocytes is restricted, which leads to negative inotropic and chronotropic effects. Overall action on the heart is depressing myocardium, which results in conduction delays, bradycardia and decreased contractility . Effect on peripheral vasculature is small or none [3].

Bisoprolol is an oral synthetic selective blocker of β_1-adrenoceptor with antioxidant activity. Due to its lipophilic nature, it penetrates into cerebrospinal fluid and therefore may exert direct regulatory effect on central neurons [4]. Bisoprolol is eliminated via renal excretion in 50% and remaining 50% are hepatically metabolised [5].

Considering benzodiazepines, the most common indications for prescription are anxiety disorders, mood disorders and insomnia [6]. Estazolam is intermediate-acting oral drug prescribed primarily for short-term treatment of insomnia[7, 8].

CASE REPORT

The 65-year-old female, was brought by emergency medical services to the Toxicology Clinic due to severe β-adrenolitic and benzodiazepine poisoning. Upon admission patient was unconscious, intubated, on respirator, in overall severe condition. Her blood pressure (BP) was 150/95 mmHg and heart ratio (HR) 40/min.

History revealed that patient ingested 30 tablets of bisoprolol a 10mg and 8 tablets of estazolam. When her son had noticed that, he informed emergency services and patient was transported to Emergency Department in local hospital. In relation of paramedics, upon arrival to patients' home, she was conscious, fully responsive, verbally communicating logically. Gastric lavage had been performed, however it did not produce expected decontaminating effect. Moreover bleeding from the nose appeared. Patients condition was worsening, she presented symptoms of circulatory insufficiency. Her heart ratio dropped to 40 per minute and blood pressure to 80/60 mmHg, therefore decision was made to transfer patient to Toxicology Clinic.

In the Toxicology Clinic, the initial pharmacological treatment included infusion of crystalloids, steroids, atropine and catecholamines. Afterwards the glucagon, calcium salts and $MgSO_4$ were used. In order to prevent circulatory collapse, keeping in mind patient's tendency towards

bradycardia, the electrode catheter was placed in the right heart. In order to stop the epistaxis the posterior nasal packing was performed. The RTG image didn't reveal problems with lungs and confirmed proper placement of intubation tube and of electrode catheter. Proceeding resulted in gradual improvement of patients condition.

Further investigation revealed that patient had great disease burden, she suffered from congestive heart failure, coronary arterial disease and underwent numerous operations in the past i.e. atrial septal defect type II surgery, coronary artery bypass, tricuspid valve repair, total histerectomy, bilateral mastectomy, partial thyroidectomy, surgery of fronto-temporal meningioma.

The blood tests including complete blood count, coagulation test, kidney function test, liver function test, venous blood gas analysis, blood sodium, potassium calcium level tests and blood glucose test remained within reference range. The only observed abnormality was mild normocytic anemia. The benzodiazepines blood concentration was 910 ng/ml, where cut off point for poisoning is >300 ng/ml. No blood alcohol was found. Echocardiographic assessment didn't reveal significant abnormalities.

On the second day, after the completion of a spontaneous breathing trial, patient was extubated. On the third day spontaneous return to sinus rhythm was observed, therefore electrostimulation was no longer necessary.

When patient was fully conscious, she underwent psychiatric and psychological assessment. Patient denied previous psychiatric treatment, psychiatric disorders running or present in family or suicidal thoughts. Those assessments did not mandate admission to a psychiatric unit. After one-week of hospitalization, the patient was discharged home in a good condition with the referral for review in cardiologic clinic.

DISCUSSION

Suicide rates in both males and females tend to increase with age [9]. The prevalence of chronic diseases and comorbidities in older patients can complicate treatment and hinder recovery.

The crucial part of assessing the patient who overdosed xenobiotic is taking a detailed history regarding co-ingestions and comorbidities. When overdosed agent remains unknown, the clues to diagnose beta blocker overdose are bradycardia associated with hypotension, assisted by altered mental status and hypoglycemia. It is important to pay attention to detailed physical examination of patients, because it may happen that besides drug overdose there may be another underlying reason for patients condition [10].

The treatment of shock usually requires a multimodal approach to improve inotropism of the heart. Current recommendations for beta-blocker toxicity medication involve glucagon, high-dose insulin and glucose, phosphodiesterase inhibitors, lipid emulsions, calcium, extracorporeal and intra-aortic balloon pump support [11]. Symptomatic bradycardia can be treated with atropine, catecholamines, glucagon and cardiac pacing.

In every case of drug intoxication aggressive gastrointestinal decontamination attempt should be considered. Choice of various methods depend mostly on time that passed since drug ingestion and type of ingested substance. Potential treatment options include activated charcoal administration, gastric lavage and whole-bowel irrigation (WBI). First two options should be used in when life-threatening overdose is suspected and less than one hour passed since ingestion [12]. The latter method may be useful in particular cases of patients who ingested drugs not adsorbed by activated charcoal, sustained-release, enteric-coated forms of drugs or if >2h have passed since drug ingestion[13]. However, WBI should be considered rather prior to the onset of symptoms. Development of hypotension and bradycardia appearance is associated with reduced bowel movements. Moreover, when sustained-release (SR) medications and longer half-lives beta-blockers are considered, patient may require extended monitoring, because peak toxicity can be delayed. 24 h period of observation in a monitored environment should be done for every asymptomatic patient with SR formulation ingestions [3].

Bisoprolol, as well as other β-blockers poses threat of overdose and drug-induced bradycardia in an elderly patient with impaired renal function and when cytochrome P450 inhibitors are used [14]. Bisocard, due to its selectivity is unlikely to cause bronchospasm, however β1-selectivity may be lost in overdose [12]. If it occurs, it may be treated with supplementation of oxygen and inhaled bronchodilators. Standard maximal recommended dose of bisocard is 10 mg.

In early stage the initial symptomatic treatment is administration of fluids and atropine. Atropine is antagonist of muscarinic acetylocholine receptor. Dosing begins with 0.5 to 1 mg I.V. every 2-3 minutes up to total dose of 3 mg. However, atropine alone is often ineffective in reversing symptoms of BB poisoning, therefore using catecholamines seems to be more reasonable in such cases [15, 18].

Glucagon can be treated as main antidote in treatment of BB poisoning. Its effects are mediated via stimulating a G protein on the β-receptor complex that increased production of cAMP. It provides moderate inotropic and chronotropic improvement, therefore especially patients with bradycardia may benefit from using it. The recommended initial dose is 5 to 10 mg in an adult, followed by an infusion from 1 to 10 mg /h. The effects of glucagon are better when it is used in conjunction with other agents [16]. Glucagon may cause nausea and vomiting, therefore premedication with antiemetic seems to be reasonable. Other side effects of this treatment are hypokalemia and hyperglycemia [17].

Calcium salts are relevant agents in BB overdosage, since such intoxication causes intracellular hypocalcemia. Administering calcium may result in improvement in blood pressure, conduction and inotropy. However they may be ineffective as single agent, and not likely to restore proper cardiovascular status by itself [19]. Infusion of calcium is not routinely recommended in BB overdosage.

In described case, since bradycardia caused by poisoning was not responsive neither to atropine stymulation, nor other agents, the electrode catheter had been placed in the right ventricle and pacing was performed to maintain proper heart rate.

Other treatment options, that may be useful if methods mentioned above do not prove to be sufficient are: High-dose insulin euglycaemic therapy, intravenous lipid emulsion and phosphodiesterase inhibitors. Some patients, especially with myocardial ischemia, may also benefit from mechanic heart support, the Intra-aortic Balloon Pump. In this method The balloon is placed in the descending thoracic aorta, below left subclavian artery. It decreases myocardial workload, improves cardiac output, blood pressure and coronary perfusion [20]. If pharmacotherapy fails to recover the patient, prompt initiation of mechanical life support i.e. ECMO may serve as bridge to recovery, until the xenobiotic effect wears off.

Number of deaths associated with benzodiazepines is growing. In USA it increased 4-fold in between 1996 and 2010 [6]. In cases of overdose, they were commonly taken together with opioids [22]. Nevertheless in this particular case the benzodiazepine poisoning played minor role. Since patient remained on the respiratory support, administration of specific treatment didn't seem to be reasonable.

CONCLUSIONS

In case of people with numerous comorbidities and serious past medical history it is important for family as well as physicians to prevent events of overdosage. If such poisoning occurs, the crucial part of treatment is rapid intervention and prompt transport to the right hospital. Due to extensive history often seen in older patients, they should be tended to by the team of experienced specialists, with equal attention given to effects of the ingested substances' toxicity as well as existing comorbidities, especially if major organs are affected. All that improves treatment outcomes and accelerates patients' recovery.

References

1. Hashiyada M, Usui K, Hayashizaki Y, Hosoya T, Igari Y, Sakai J, et al. Unexpectedly high blood concentration of bisoprolol after an incorrect prescription: A case report. Leg Med. 2013;15(2):103–5.

2. DeWitt CR, Waksman JC. Pharmacology, pathophysiology and management of calcium channel blocker and beta-blocker toxicity. Toxicol Rev. 2004;23(4):223–38.

3. Graudins A, Lee HM, Druda D. Calcium channel antagonist and beta-blocker overdose: antidotes and adjunct therapies. Br J Clin Pharmacol. 2016;81(3):453–61.

4. Sigaroudi A, Kinzig M, Wahl O, Stelzer C, Schroeter M, Fuhr U, et al. Quantification of Bisoprolol and Metoprolol in Simultaneous Human Serum and Cerebrospinal Fluid Samples. Pharmacology. 2018;101(1–2):29–34.

5. Brodde O-E, Kroemer H. Drug-Drug Interactions of β-Adrenoceptor Blockers. Arzneimittelforschung. 2011;53(12):814–22.

6. Bachhuber MA, Hennessy S, Cunningham CO, Starrels JL. Increasing Benzodiazepine Prescriptions and Overdose Mortality in the United States, 1996–2013. Am J Public Health. 2016;106(4):686–8.

7. Almoznino G, Haviv Y, Sharav Y, Benoliel R. An update of management of insomnia in patients with chronic orofacial pain. Oral Dis. 2017;23(8):1043–51.

8. Mancinelli A, Guiso G, Garattini S, Urso R, Caccia S. Kinetic and pharmacological studies on estazolam in mice and man. Xenobiotica. 1985;15(3):257–65.

9. Vijayakumar L. Suicide in women. Indian J Psychiatry. 2015;57(Suppl 2):S233-8.

10. Ramdas S, Riesenberg LA, Jasani N. Drug overdose with refractory bradycardia and hypotension. Del Med J. 2011;83(6):169–72.

11. Truhlář A, Deakin CD, Soar J, Khalifa GEA, Alfonzo A, Bierens JJLM, et al. European Resuscitation Council Guidelines for Resuscitation 2015. Resuscitation. 2015;95:148–201.

12. Shepherd G. Treatment of poisoning caused by β-adrenergic and calcium-channel blockers. Am J Heal Pharm. 2006;63(19):1828–35.

13. Thanacoody R, Caravati EM, Troutman B, Höjer J, Benson B, Hoppu K, et al. Position paper update: Whole bowel irrigation for gastrointestinal decontamination of overdose patients. Clin Toxicol. 2015;53(1):5–12.

14. Lafarge L, Bourguignon L, Bernard N, Vial T, Dehan-Moya M-J, De La Gastine B, et al. Facteurs de risque pharmacocinétiques de surdosage en bêta-bloquants chez les patients âgés : cas clinique et rationnel pharmacologique. Ann Cardiol Angeiol (Paris). 2018;67(2):91–7.

15. Taboulet P, Cariou A, Berdeaux A, Bismuth C. Pathophysiology and management of self-poisoning with beta-blockers. J Toxicol Clin Toxicol. 1993;31(4):531–51.

16. Bailey B. Glucagon in beta-blocker and calcium channel blocker overdoses: a systematic review. J Toxicol Clin Toxicol. 2003;41(5):595–602.

17. Peterson CD, Leeder JS, Sterner S. Glucagon therapy for beta-blocker overdose. Drug Intell Clin Pharm. 1984;18(5):394–8.

18. Jang DH, Spyres MB, Fox L, Manini AF. Toxin-Induced Cardiovascular Failure. Emerg Med Clin North Am. 2014;32(1):79–102.

19. Walter E, McKinlay J, Corbett J, Kirk-Bayley J. Review of management in cardiotoxic overdose and efficacy of delayed intralipid use. J

Intensive Care Soc. 2018;19(1):50.

20. van Nunen LX, Noc M, Kapur NK, Patel MR, Perera D, Pijls NHJ. Usefulness of Intra-aortic Balloon Pump Counterpulsation. Am J Cardiol. 2016;117(3):469–76.

21. Mégarbane B, Deye N, Malissin I, Baud FJ. Usefulness of the serum lactate concentration for predicting mortality in acute beta-blocker poisoning. Clin Toxicol. 2010;48(10):974–8.

22. Jones CM, McAninch JK. Emergency Department Visits and Overdose Deaths From Combined Use of Opioids and Benzodiazepines. Am J Prev Med. 2015;49(4):493–501.