Acta Clin Croat 2024; 63:816-821
doi: 10.20471/acc.2024.63.03-04.45

Case Report

PHEOCHROMOCYTOMA CRISIS TREATED WITH URAPIDIL: A CASE REPORT

Miro Bakula[1], Lea Tomašić[2], Ivana Kokan[2], Katarina Mucić[2], Nikolina Marić[3] and Maja Bakula[4]

[1] Sveti Duh University Hospital, Division of Endocrinology, Department of Internal Medicine, Zagreb, Croatia;
[2] graduate student, School of Medicine, University of Zagreb, Zagreb, Croatia;
[3] Sveti Duh University Hospital, Department of Intensive Care, Zagreb, Croatia;
[4] Merkur University Hospital, University Clinic for Diabetes, Endocrinology and Metabolic Diseases, Zagreb, Croatia

SUMMARY – Pheochromocytomas are rare tumors that present with a broad spectrum of symptoms and signs, making differential diagnosis broad. They can cause a pheochromocytoma crisis that manifests with arterial blood pressure oscillations, and subsequent symptoms and signs of catecholamine overproduction. There are many potential triggers of this condition. This report presents a 33-year-old man with an obvious pheochromocytoma crisis that occurred due to beta-blocker application without a concomitant alpha-blocker. The crisis was treated with high doses of urapidil, and once permanent hemodynamic stabilization was achieved, urapidil was replaced with phenoxybenzamine. This report demonstrates that pheochromocytoma crisis can be successfully treated with urapidil but further consideration is needed on the use of urapidil both in pheochromocytoma crisis and preoperative management of pheochromocytoma patients.

Keywords: *Pheochromocytoma; Hypertensive crisis; Urapidil*

Introduction

Pheochromocytoma is a rare catecholamine-producing tumor originating mainly in the adrenal gland medulla, occuring in less than 0.1% of all hypertensive individuals. It is typically sporadic but up to 25% of cases can be associated with autosomal dominant genetic syndromes such as Von Hippel Lindau disease, multiple endocrine neoplasia type 2 (MEN2) and neurofibromatosis type 1[1]. Hypertension is the most common symptom of pheochromocytoma, often accompanied by tachycardia, palpitations, and sweating. Due to the tumor intermittent secretion of cathecholamines, pheochromocytoma can cause pheochromocytoma crisis when large quantities of catheholamines are released into the circulation. It is a rare, life-threatening condition presenting as hemodynamic instability followed by potential multiple organ failure. Pheochromocytoma crisis must be promptly managed with alpha-blockers. The alpha-blocker urapidil has previously only been used peri- and intraoperatively in adrenalectomy due to pheochromocytoma. In this report, for the first time to our knowledge, we

Correspondence to: *Miro Bakula, MD, PhD,* Sveti Duh University Hospital, Division of Endocrinology, Department of Internal Medicine, Sveti Duh 64, 10000 Zagreb, Croatia
E-mail: mbakula@kbsd.hr

Received November 3, 2021, accepted December 1, 2021

investigated the efficacy of urapidil in managing pheochromocytoma crisis.

Case Report

A 33-year-old Caucasian man was admitted to the emergency department (ED) presenting with blood pressure (BP) and heart rate (HR) oscillations accompanied by occipital headache. He had been diagnosed with hypertension two months before when antihypertensive therapy was prescribed. BP values had been well controlled until ten days before when BP values suddenly increased, hence antihypertensive therapy was modified by adding bisoprolol 2.5 mg to the earlier fixed-dose combination of perindopril/indapamide/amlodipine 10 mg/2.5 mg/10 mg. During ED examination, the patient's BP values varied from 140/90 mm Hg to 200/100 mm Hg, and HR from 60/min to 120/min in a short period of time. As the patient's current status along with a history of tingles in both hands, nausea, sweating and palpitations suggested adrenal gland disorder, an abdominal computed tomography (CT) scan was performed, revealing a tremendous mass in the left suprarenal adrenal gland, measuring 7 cm in diameter, with remarkable postcontrast imbibition (Fig. 1).

Radiomorphological characteristics, along with symptoms, suggested the lesion to be a pheochromocytoma. Because of the need of strict monitoring of

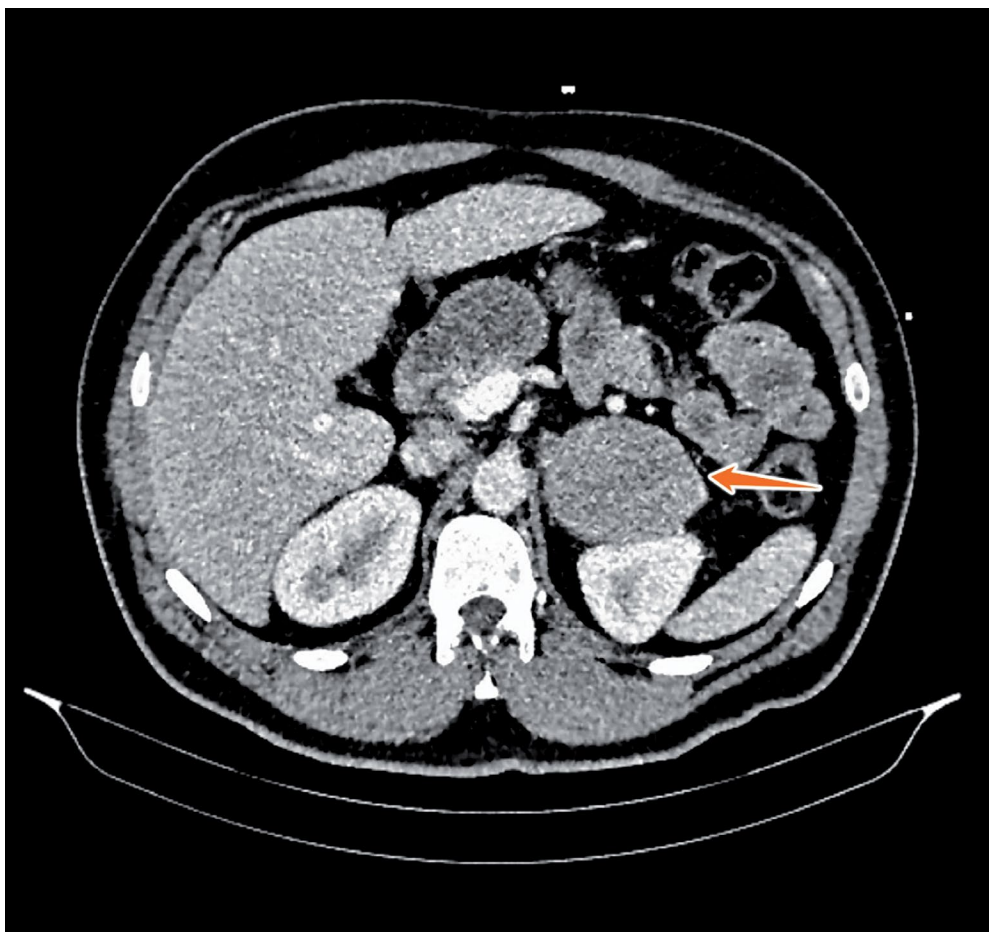

Fig. 1. Adrenal mass as seen on abdominal computed tomography.

the clinical condition and detailed diagnostic and therapeutic procedures, the patient was admitted to the intensive care unit (ICU). An arterial line was inserted for continuous invasive BP (ABP) measurement along with continous monitoring of heart rhythm. Collection of urine for cathecholamine assessment was initiated. At ICU admision, the patient had elevated but stable ABP levels without specific symptoms. Then suddenly, approximately 12 hours post admission, he became hemodynamically and clinically unstable with rapid alterations of ABP from 320/180 mm Hg to 70/40 mm Hg (Fig. 2). Hypertensive episodes were accompanied by bradycardia (up to 40/min) and hypotensive episodes with supraventricular tachycardia (up to 150/min). The hypertensive and hypotensive episodes alternated and each lasted for several minutes. During these huge oscillations in ABP and HR, the patient experienced headache, nausea and vomiting, dizziness and profuse sweating.

In this patient, pheochromocytoma crisis developed due to administration of the beta-blocker bisoprolol 10 days prior to hospitalization without concomitant use of an alpha-blocker. Considering the etiopathologic mechanism, crisis treatment was initiated immediately. During hypertensive episodes, the patient was administered the alpha-blocker urapidil by intravenous (IV) infusion, i.e., 100 mg of urapidil diluted in 50 mL of normal saline by a syringe pump with flow rate titrated according to the ABP (average flow 3 mg/min, maximal 5 mg/min). In

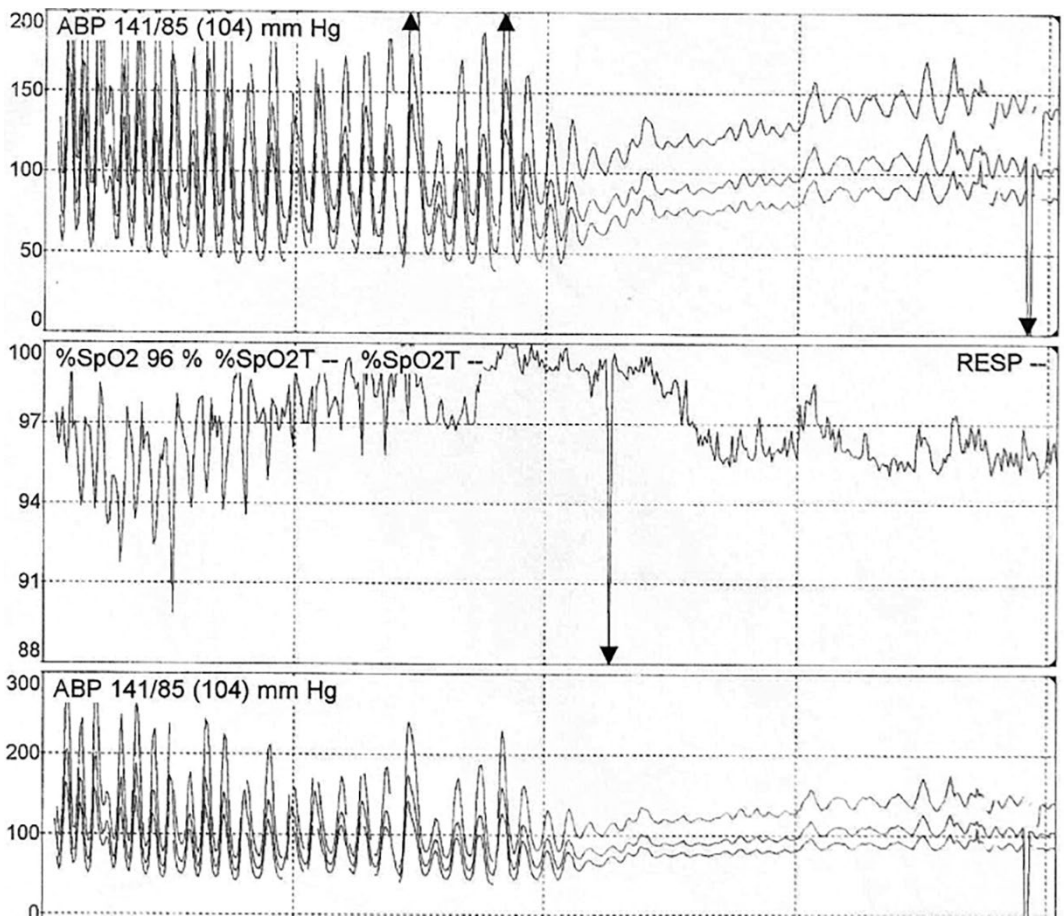

Fig. 2. Blood pressure fluctuations during pheochromocytoma crisis.

hypotensive episodes, urapidil infusion was turned off and replaced with rapid cristalloid IV infusion. Prior to every increase in ABP, tachycardia occurred, and *vice versa*. With these changes in heart rhythm, we were able to predict ABP changes and titrate therapy according to these alterations. Urapidil and cristalloid infusion were alternated according to invasively monitored ABP values and heart rhythm for several hours. When a high cummulative dose of urapidil was administered (approximately 600 mg), the IV beta-blocker esmolol was administered, followed by oral administration of propranolol four times a day. After four hours of extreme instability, hemodynamic stabilization was achieved and pheocromocytoma crisis ended.

When the crisis was terminated, ABP values were initially regulated with continuous infusion of urapidil (100 mg diluted in 50 mL of normal saline administerd by a syringe pump with an average flow rate of 15 mg/h) and propranolol tablets *per os*. On day 4, oral phenoxybenzamine was added to the regimen with withdrawal of urapidil infusion as ABP values stabilized. During pheochromocytoma crisis, 24 h urine was collected. Metanephrine levels in that 24-h urine sample were 237.9 mcmol/dU (reference range <2.0), and normetanephrine levels were 165.8 mcmol/dU (reference range <4.4), which confirmed the pheochromocytoma diagnosis. Genetic testing excluded the possibility of MEN2 syndrome. As the diagnosis was confirmed, the patient was scheduled for adrenalectomy. While he was waiting for surgery, he was taking phenoxybenzamine 30 mg three times a day, and propranolol four times a day in doses of 30 mg, 30 mg, 20 mg and 10 mg. Taking these medications was sufficient to keep the patient's BP and HR consistent. Fifteen days after pheochromocytoma crisis, the patient was transferred from the Sveti Duh University Hospital to the Zagreb University Hospital Center to undergo left laparoscopic adrenalectomy. Surgery went well and the tumor was removed entirely. Six weeks postoperatively, the patient was feeling well and had well regulated BP. Newly-collected urine metanephrine levels were 0.4 mcmol/dU and normetanpehrine 3.8 mcmol/dU, both within the normal range. Chromogranin A level was 25.0 ng/L (reference range <39.0 ng/L), which suggested biochemical remission. Histopathologic diagnosis showed the tumor was a pheochromocytoma, with morphological characteristics of a biologically aggressive disease (PASS score 12/20, Ki-67 up to 20%).

Discussion

Pheochromocytoma crisis is a rare condition[2,6] caused by the tumor excessive adrenaline stimulation of alpha-adrenergic receptors. Many factors can precipitate pheochromocytoma crisis[7]. Non-pharmacological causes include bleeding, surgical manipulation or biopsy, physical trauma in the tumor area, pregnancy, and hypoxic conditions. There are many medications that are possible triggers, especially dopaminergic antagonists, beta-blockers without the use of alpha-blockers, and muscle relaxants. Less common causes of pheochromocytoma crisis include glucagon, sympathomimetics, synthetic adrenocorticotropic hormone, tricyclic antidepressants or radiological contrast use[6]. The cause of pheochromocytoma crisis in our patient was the use of beta-blockers (prescribed with the aim of hypertension regulation) without concomitant use of an alpha-blocker. According to the literature, optimal crisis management differs and represents a true challenge for physicians. There are multiple case reports where treatment with alpha-blockers was successful[2-6]. In the majority of literature reports, the non-selective alpha-blocker phenoxybenzamine was used[3,8]. It can be administered orally, intravenously or *via* a nasogastric tube, with an initial IV dose of 0.5 mg/kg over the course of five hours[6]. Despite successful treatment of the crisis, it should be considered that phenoxybenzamine is associated with numerous side effects, most significantly orthostatic hypotension and reflex tachycardia[8,9]. Moreover, in comparison to selective alpha-blockers, it causes significant BP fluctuations[3]. Successful crisis management has been recorded using phentolamine[3,6,10]. It is given slowly by IV administration of 1 mg/min and is recommended in cases of complicated pheochromocytoma crisis, such as crisis associated with thyrotoxic crisis[4] and Takotsubo cardiomyopathy[10] because of its rapid efficacy[6]. New guidelines recommend phentolamine when BP oscillations are extremely high[11]. One of the oldest medicines used for pheochromocytoma crisis stabilization is magnesium sulfate. It dilates arterioles

affecting calcium channels, inhibits catecholamine secretion, and has an antiarrhythmic effect. Magnesium sulfate, once the drug of choice for treating pheochromocytoma crisis, is now being increasingly replaced by new alpha-blockers[6]. Calcium channel blockers are less frequently used in the treatment of this disorder but there are successful cases of crisis treatment only with calcium channel blockers such as nicardipine and clevidipine[6]. They are used more often with other drugs in treating complicated conditions like combined pheochromocytoma and thyrotoxic crisis[4]. There are several described cases of pheochromocytoma crisis treated with doxazosin[6], but it has mostly been described as a preoperative agent in patients with stable pheochromocytoma[12].

Conclusion

This case report describes successful treatment of pheochromocytoma crisis with the alpha-blocker urapidil. It has been described as the drug used in preoperative management of pheochromocytoma and as prophylaxis of hypertension caused by tumor catecholamines[8,13]. The drug affects blood vessel alpha receptors and has effects on the central nervous system[14]. It has been proven as a successful drug in the preoperative management of patients with pheochromocytoma with the purpose of hypertension prevention and heart failure prevention during surgical removal of the tumor[13,14]. In this case report, for the first time to our knowledge, we describe successful management of pheochromocytoma crisis with urapidil. Even though urapidil has been used previously for hypertensive crisis, it has never been used for pheochromocytoma crisis, as shown here. We recommend slow titration of parenteral urapidil until high doses are reached. After administration of high doses of urapidil, administration of beta-blockers (e.g., bisoprolol) is recommended as prevention of repeated hemodynamic instability caused by the tumor catecholamines. After reaching stable BP for a couple of days, parenteral urapidil can be replaced with oral phenoxybenzamine. Further research is needed to distinguish whether urapidil is unequivocally better than phenoxybenzamine as first-line medication for treating pheochromocytoma crisis.

References

1. Farrugia FA, Martikos G, Tzanetis P, Charalampopoulos A, Misiakos E, Zavras N, Sotiropoulos D. Pheochromocytoma, diagnosis and treatment: review of the literature. Endocr Regul. 2017 Jul 1;51(3):168-81. doi: 10.1515/enr-2017-0018.
2. Farrugia FA, Charalampopoulos A. Pheochromocytoma. Endocr Regul. 2019;53(3):191-212. doi: 10.2478/enr-2019-0020.
3. Larouche V, Garfield N, Mitmaker E. Extreme and cyclical blood pressure elevation in a pheochromocytoma hypertensive crisis. Case Rep Endocrinol. 2018;2018:4073536. doi: 10.1155/2018/4073536.
4. Suzuki K, Miyake T, Okada H, Yamaji F, Kitagawa Y, Fukuta T, *et al*. Thyrotoxic and pheochromocytoma multisystem crisis: a case report. J Med Case Rep. 2017;11(1):173. doi: 10.1186/s13256-017-1299-y.
5. Wu R, Tong N, Chen X, *et al*. Pheochromocytoma crisis presenting with hypotension, hemoptysis, and abnormal liver function: a case report. Medicine (Baltimore). 2018;97(25) :e11054. doi:10.1097/MD.0000000000011054
6. Whitelaw BC, Prague JK, Mustafa OG, Schulte KM, Hopkins PA, Gilbert JA, *et al*. Pheochromocytoma crisis. Clin Endocrinol (Oxf). 2014;80(1):13-22. doi: 10.1111/cen.12324.
7. Sibal L, Jovanovic A, Agarwal SC, Peaston RT, James RA, Lennard TW, *et al*. Phaeochromocytomas presenting as acute crises after beta blockade therapy. Clin Endocrinol (Oxf). 2006;65(2):186-90. doi: 10.1111/j.1365-2265.2006.02571.x.
8. Rončević T, Zeljković-Vrkić T, Kos J, Fištrek M. Feokromocitom – dijagnostički i terapijski izazov koji traje. Medicus. 2017;16(2):205-10. (in Croatian)
9. Yoham AL, Casadesus D. Phenoxybenzamine. StatPearls [Internet]. https://www.ncbi.nlm.nih.gov/books/NBK560667/. Updated November 30, 2020. Accessed January 7, 2021.
10. Casey RT, Challis BG, Pitfield D, Mahroof RM, Jamieson N, Bhagra CJ, *et al*. Management of an acute catecholamine-induced cardiomyopathy and circulatory collapse: a multidisciplinary approach. Endocrinol Diabetes Metab Case Rep. 2017;2017:17-0122. doi: 10.1530/EDM-17-0122.
11. Leonard JB, Munir KM, Kim HK. Metoclopramide induced pheochromocytoma crisis. Am J Emerg Med. 2018;36(6):1124. e1-1124.e2. doi: 10.1016/j.ajem.2018.03.009.
12. Iglesias P, Santacruz E, García-Sancho P, Marengo AP, Guerrero-Pérez F, Pian H, *et al*. Pheochromocytoma: a three-decade clinical experience in a multicenter study. Rev Clin Esp. 2020; S0014-2565(20)30114-4. doi: 10.1016/j.rce.2019.12.016.

13. Habbe N, Ruger F, Bojunga J, Bechstein WO, Holzer K. Urapidil in the preoperative treatment of pheochromocytomas: a safe and cost-effective method. World J Surg. 2013 May;37(5):1141-6. doi: 10.1007/s00268-013-1933-9.

14. Minushkina LO. Treatment of hypertensive emergencies and malignant hypertension: the possibility of using urapidil. Kardiologiia. 2014;54(11):70-4. doi: 10.18565/cardio.2014.11.70-74. (in Russian)

Sažetak

FEOKROMOCITOMSKA KRIZA LIJEČENA URAPIDILOM: PRIKAZ SLUČAJA

M. Bakula, L. Tomašić, I. Kokan, K. Mucić, N. Marić i *M. Bakula*

Feokromocitomi su rijetki tumori koji se manifestiraju širokim spektrom simptoma i znakova, što uvjetuje široku diferencijalnu dijagnostiku. Oni pak mogu uzrokovati feokromocitomsku krizu koja se očituje oscilacijama arterijskog krvnog tlaka te naknadnim simptomima i znakovima prekomjernog stvaranja katekolamina. Mnogo je potencijalnih okidača ovoga stanja. Ovdje prikazujemo slučaj muškarca u dobi od 33 godine s očitom feokromocitomskom krizom koja je nastupila zbog primjene beta blokatora bez istodobne promjene alfa blokatora. Ovu krizu liječili smo visokim dozama urapidila, a kad je postignuta trajna hemodinamska stabilizacija, urapidil je zamijenjen fenoksibenzaminom. Ovaj prikaz slučaja dokazuje da je feokromocitomsku krizu moguće uspješno liječiti urapidilom, ali pritom valja razmotriti primjenu urapidila i zbog feokromocitomske krize i kao prijeoperacijsko liječenje bolesnika s feokromocitomom.

Ključne riječi: *Feokromocitom; Hipertenzivna kriza; Urapidil*