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CASE REPORTS / CASE SERIES

Failure of metyrosine therapy for preoperative management of pheochromocytoma: a case report

Échec du traitement par métyrosine pour la gestion préopératoire d'un phéochromocytome: une étude de cas

Kabilan Thanapaalasingham, BSc · André S. Pollmann, BScPharm · Benjamin Schelew, MD

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Abstract

Purpose *Pheochromocytomas (PHEOS) are rare catecholamine-secreting adrenal tumours requiring surgical resection. Preoperative alpha-adrenergic receptor blockade to prevent intraoperative hypertension has traditionally been achieved with phenoxybenzamine. Due to changes in the availability of phenoxybenzamine in Canada, alternate therapies are needed for patients. We report our first experience using metyrosine, a tyrosine hydroxylase inhibitor, for preoperative management in a symptomatic patient with a unilateral PHEO.*

Clinical features *A 50-yr-old male was referred to our centre with a history of symptoms suggestive of a catecholamine-secreting PHEO, including tachycardia, diaphoresis, nervousness, and tremor. Computerized tomography revealed a right adrenal mass, and additional positive imaging and elevated urine epinephrine levels supported a diagnosis of PHEO. The patient was admitted to hospital five days prior to surgery, and metyrosine therapy was initiated and titrated to 4 g daily over four days. Despite adequate blood pressure (BP) control leading up to the resection, the initial BP reading in the operating room was 191/106 mmHg, but it subsequently declined and was well controlled during induction (100-110 mmHg systolic BP). Significant hypertension (up to 201/110 mmHg) developed upon tumour manipulation and resolved with phentolamine administration and surgical isolation of the tumour. The patient's BP remained stable throughout the residual part of the procedure and in the recovery room and step-down unit.*

Conclusion *In the case of this patient's PHEO, the use of metyrosine was unsatisfactory in achieving sufficient inhibition of catecholamine synthesis as evidenced by significant intraoperative hypertension. Metyrosine could have a role in preoperative management of these patients, but it may not be optimal as monotherapy for some patients with actively secreting tumours.*

Résumé

Objectif *Les phéochromocytomes sont des tumeurs corticosurrénaliennes rares sécrétrices de catécholamines qui nécessitent une résection chirurgicale. Le blocage préopératoire des récepteurs alpha-adrénergiques est habituellement obtenu avec de la phénoxybenzamine afin de prévenir une hypertension peropératoire. Compte tenu des modifications dans la disponibilité de la phénoxybenzamine au Canada, des traitements de substitution sont nécessaires pour les patients. Nous décrivons notre première expérience d'utilisation de la métyrosine, un inhibiteur de la tyrosine hydroxylase pour la gestion préopératoire d'un patient ayant un phéochromocytome unilatéral symptomatique.*

Author contributions *Kabilan Thanapaalasingham* coordinated the project, was responsible for data collection and analysis, drafted the manuscript, and provided critical feedback. *André Pollmann* assisted in the study conceptualization, coordination, and data collection aspects of the project. He was responsible for submitting the manuscript for publication. *Benjamin Schelew* conceptualized the study and supervised the data collection and clinical aspects of the project. *Benjamin Schelew* and *André Pollmann* drafted parts of the manuscript and contributed critical revisions.

K. Thanapaalasingham, BSc ·
A. S. Pollmann, BScPharm (✉) · B. Schelew, MD
Department of Anesthesia, Pain Management and Perioperative Medicine, Dalhousie University, Halifax, NS, Canada
e-mail: andre.p@dal.ca

B. Schelew, MD
Department of Anesthesia, Queen Elizabeth II Health Science Centre, Halifax, NS, Canada

Caractéristiques cliniques *Un homme âge de 50 ans a été adressé à notre centre avec un ensemble de symptômes (tachycardie, diaphorèse, nervosité, et tremblement) faisant évoquer un phéochromocytome avec sécrétions de catécholamines. Une tomodensitométrie a révélé une masse dans la corticosurrénale droite et une imagerie positive supplémentaire et des taux urinaires élevés d'épinéphrine étayaient un diagnostic de phéochromocytome. Le patient a été hospitalisé cinq jours avant la date de l'intervention chirurgicale et un traitement par métyrosine a été entrepris, puis augmenté à 4 g/j pendant 4 jours. En dépit d'un contrôle adéquat de la pression artérielle (PA) jusqu'à la résection, la valeur initiale de la PA en salle d'opération était de 191/106 mmHg; elle a ensuite baissé et a été bien contrôlée pendant la phase d'induction (PA systolique : 100-110 mmHg). Une hypertension significative (jusqu'à 201/110 mmHg) est apparue au moment de la manipulation de la tumeur et a ensuite disparu avec l'administration de phentolamine et l'isolement chirurgical de la tumeur. La PA du patient est restée stable pendant tout le reste de l'intervention ainsi que pendant le séjour en salle de réveil et en unité de convalescence.*

Conclusion *Dans le cas du phéochromocytome de ce patient, l'utilisation de la métyrosine n'a pas permis d'obtenir une inhibition suffisante de la synthèse de catécholamine comme l'a montré l'hypertension peropératoire significative. La métyrosine pourrait jouer un rôle dans la gestion préopératoire de ces patients, mais cela ne pourrait pas être optimal en monothérapie chez les patients ayant une tumeur à forte activité sécrétoire.*

Pheochromocytomas (PHEOS) are relatively rare catecholamine-secreting tumours arising from chromaffin cells of the adrenal medulla and are often discovered incidentally on imaging studies or at autopsy.[1,2] Although treatment with antihypertensives can improve symptoms, definitive treatment requires surgical resection. An important component of preoperative management involves drug therapy to block peripheral alpha-adrenergic receptors and thus prevent hypertension from catecholamine release during surgical manipulation of the tumour.[1,3] Phenoxybenzamine, an oral, irreversible, and non-specific alpha-adrenergic blocker, has been the most widely utilized agent for this purpose, and its use has been attributed to improved surgical outcomes over the past decades in patients undergoing PHEO resection.[3-5]

Phenoxybenzamine was available until recently through Health Canada's Special Access Programme; however, in October 2014, the manufacturer and supplier of the product in Canada, WellSpring Pharmaceuticals, divested the rights to phenoxybenzamine to Covis Pharmaceuticals, who distribute their products only within Europe and the United States. Canadian hospitals are therefore left without access to phenoxybenzamine and will need to turn to alternate preoperative treatments when managing patients with PHEOS. Currently, other options for adrenergic blockade include competitive alpha-1 receptor antagonists (e.g., prazosin, terazosin, doxazosin) and metyrosine. Metyrosine exerts its antihypertensive action by inhibiting tyrosine hydroxylase, therefore preventing endogenous catecholamine synthesis.[3] Nevertheless, clinical experience with these options is limited in comparison with phenoxybenzamine. Herein, we report on our first experience using metyrosine prior to surgical resection of a symptomatic PHEO and discuss relevant treatment implications and considerations.

Case

The patient gave his consent for publication of this case. A 50-yr-old male (height, 178 cm; weight, 88 kg; body mass index, 27.8 $kg \cdot m^{-2}$) was admitted for resection of a unilateral PHEO after he presented with classical findings of this tumour. Following a ten-year history of essential hypertension, he had experienced worsening hypertension accompanied by increasing intermittent episodes of nervousness, tremor, and diaphoresis over the past year. These episodes occurred especially when he was fatigued and/or stressed. In addition to symptoms, a suspicious 3.2-cm right adrenal mass had been discovered incidentally on a follow-up computerized tomography scan for sarcoidosis about four months prior to our involvement. A 24-hr urine catecholamine analysis revealed an epinephrine excretion of 591 μg (normal reference range: 0-25 $\mu g \cdot 24\ hr^{-1}$). Positive gadolinium-enhanced magnetic resonance imaging and radiopharmaceutical metaiodobenzylguanidine investigation further supported the diagnosis of PHEO.

Additional medical history included a pulmonary embolism and two deep vein thromboses leading to a diagnosis of factor V Leiden deficiency. The patient had received a previous general anesthetic for a knee arthroscopy without complications but had experienced intraoperative hypertension during sarcoid lymph node excision the year prior. His current medications included valsartan 360 mg daily, diltiazem 120 mg daily, hydrochlorothiazide 12.5 mg daily, rivaroxaban 20 mg daily, and terazosin 2 mg twice daily. There was no known family history suggestive of PHEOS.

While awaiting surgical consultation, the patient presented to the emergency department with chest discomfort, hypertension (170/110 mmHg), and

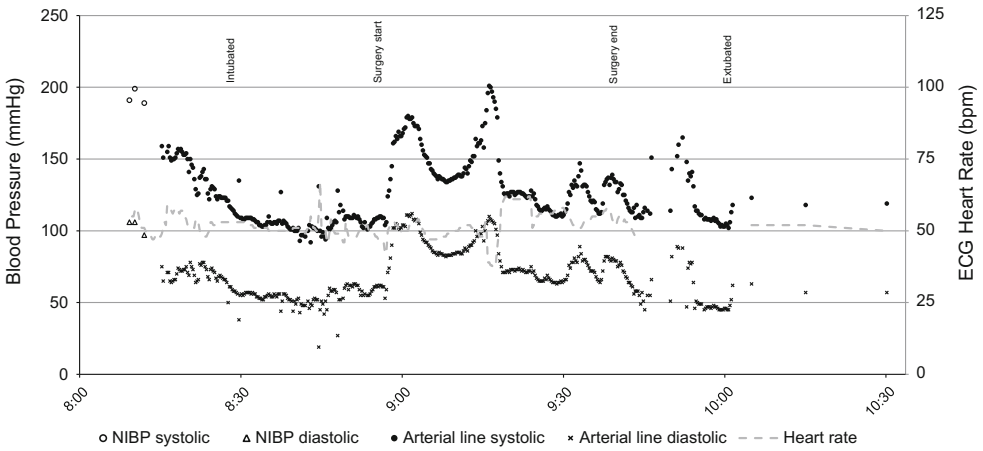

Figure Intraoperative hemodynamic data. NIBP = noninvasive blood pressure; ECG = electrocardiogram

tachycardia (> 130 beats·min^{-1}) two weeks prior to our involvement. Investigation with electrocardiogram, cardiac enzymes, and exercise stress test did not find any evidence of cardiac ischemia. The patient was promptly referred for laproscopic right adrenalectomy.

Upon hospital admission, the patient's blood pressure (BP) was 142/80 mmHg with no postural drop. We initiated metyrosine at 250 mg four times daily and monitored his BP. The dose was increased by 1 g each day for a total of 1 g for the first day, 2 g for the second day, 3 g for the third day, and 4 g for days four and five preoperatively. At the time of starting metyrosine, we discontinued his hydrochlorothiazide, valsartan, and terazosin to allow for the upward titration of metyrosine. On day 3, the patient's heart rate was still in the mid-50s. We then discontinued his diltiazem in the hopes that his heart rate would increase and allow us to initiate beta-blocker therapy, knowing that this was an epinephrine-secreting tumour. Twenty-four hours before surgery, labetalol was begun at 100 mg twice daily (total of three doses administered). The patient experienced a significant degree of somnolence but was never found difficult to arouse. We did not establish a postural drop in his BP at any time preoperatively, although there was a downward trend over the five days.

The patient entered the operating room and standard Canadian Anesthesiologists' Society monitors were applied.[6] Detailed intraoperative hemodynamic data are presented in the Figure. His initial BP in the operating room was 191/106 mmHg, but after he was given midazolam 2 mg and fentanyl 50 μg, the systolic BP eased down to 160 mmHg without further intervention. Given this hypertensive presentation, the patient was given magnesium sulfate 2 g pre-induction, and following pre-oxygenation, he was given further fentanyl 150 μg as well as lidocaine 50 mg, propofol 200 mg in divided doses, and rocuronium 40 mg. Laryngoscopy and tracheal intubation did not provoke a hypertensive response, with systolic pressure remaining at 100-110 mmHg. To maintain anesthesia, we used 1 to 1.5 minimum alveolar concentration sevoflurane and boluses of rocuronium titrated to the patient's train of four response. An impressive BP reaction to pneumoperitoneum (180/111 mmHg) occurred during the procedure; however, a bolus of remifentanil offset this response, reducing systolic BP to 130-135 mmHg until tumour manipulation. At this point, the patient's BP rose to 201/110 mmHg but resolved with a bolus of phentolamine 5 mg and surgical isolation of the tumour. He received a total of 1.5 mg of hydromorphone, and he also received neostigmine and glycopyrrolate for reversal. His pressure remained stable throughout the residual part of the procedure and in the recovery room and step-down unit. The total time for the surgical procedure was 42 min.

The postoperative pathologic investigation of the right adrenal gland was consistent with the diagnosis of PHEO with a maximum neoplasm dimension of 3.7 cm and a mass of 26 g.

Discussion

Metyrosine exerts an inhibitory effect on tyrosine hydroxylase, the rate-limiting step in catecholamine biosynthesis. The result is a decrease in circulating catecholamine levels by 50-80%, with maximal response achieved within two or three days of administration.[7,8] This is clinically monitored by observing a reduction in BP. The commonly accepted dosing schedule for metyrosine begins at 250 mg four times daily on the first day of administration and increases by 1 g daily until reaching a maximum dose of 4 g per day.[9] Pharmacokinetic parameters include a Cmax of one to three hours and a half-life of 3.4 - 3.7 hr.[7] Metabolism is primarily renal, and up to 88% of a dose is excreted unchanged in the urine.

The main adverse effect of metyrosine is somnolence, and up to 96% of patients experience varying degrees of sedation.[7] This is a dose-dependent effect, with patients

reporting persistent somnolence at doses exceeding 2 g per day. As metyrosine reduces circulating dopamine levels, patients may develop depressive mood, galactorrhea and, rarely, extrapyramidal signs (e.g., parkinsonism).[8,10] The most concerning adverse effect, however, is crystalluria, and patients should maintain a high fluid intake to avoid this outcome.[7]

Our search for an alternate form of preoperative management stemmed from the recent unavailability of phenoxybenzamine in Canada. Our options for alternative management were other methods of alpha-1 receptor blockade (e.g., doxazosin, prazosin, tamsulosin) and catecholamine biosynthesis inhibitors (e.g., metyrosine). As alternative forms of alpha-1 blockade are competitive antagonists, any catecholamine surges resulting from tumour manipulation during resection could displace the drug from the receptor and increase the risk for hypertensive crisis.[9,11]

In many studies, metyrosine has been used concomitantly with alpha-1 blockade—primarily phenoxybenzamine—in the preoperative management of PHEOS. In retrospective studies, this combination of metyrosine and alpha blockade has been associated with resections that required less volume and pressure control compared with the classical method of single-agent adrenergic blockade.[12,13] There have been instances of successful metyrosine therapy in preoperative management of routine cases[7] and in patients resistant to alpha blockade.[14] Nevertheless, a case of perioperative hypertensive crisis has been reported following management with metyrosine alone.[15] Increased activity of an alternate catecholamine pathway following metyrosine therapy may account for this incidence.[16]

Our review of the literature and our previous clinical experience with preoperative preparation of PHEOS guided our choice to use metyrosine alone without concomitant *selective* competitive alpha-1 blockade—keeping in mind that we did use labetalol, which exerts beta-alpha antagonism in a 3:1 ratio after oral administration.[17,18] While practices in preparation for surgical treatment of malignant PHEOS vary at each institution, we recognize that recent research and review articles suggest that metyrosine is ideally used in combination with alpha blockade, including either competitive or non-competitive agents.[10,11,13] Still, a review of older reports suggests that metyrosine monotherapy is a suitable option for achieving perioperative BP control in both malignant and benign PHEOS.[7] Although one case report indicated that metyrosine had not been effective as a sole agent,[15] similar reports exist for phenoxybenzamine monotherapy.[13] As with metyrosine, we had no prior experience using competitive alpha-1 antagonists preoperatively for PHEOS at our institution. As this case is our first experience preparing a patient for PHEO resection in the absence of phenoxybenzamine, we sought to develop clinical experience and observe if metyrosine could act as a sole replacement for phenoxybenzamine.

Our experience with metyrosine in this case was less than ideal when compared with our previous experiences with phenoxybenzamine. We had anticipated a more significant reduction in preoperative BP as well as development of some postural hypotension. Nevertheless, our patient's history of essential hypertension and the discontinuation of his antihypertensives created some uncertainty in interpreting the response. Another consideration for interpreting our report is the use of labetalol, which exerts mixed alpha- and beta-receptor antagonism. At our institution, labetalol administration has historically been a common component of preoperative management of PHEOS.

The intraoperative response in BP to tumour resection suggests that metyrosine had not adequately inhibited catecholamine synthesis, even at the maximum recommended dose. The degree of intraoperative fluctuation, although not prolonged and manageable with phentolamine, had seldom been observed in our experience managing PHEOS with phenoxybenzamine. Nevertheless, given the variability between PHEO cases, the degree of intraoperative hemodynamic instability may well have been within a normal expected range.[3]

In retrospect, our patient's preoperative management may have been handled differently in order to produce a more optimal outcome. First, while we administered a bolus dose of magnesium sulfate, other authors have described continuing a magnesium sulfate infusion throughout the entire surgery.[19-21] Magnesium sulfate is thought to stabilize hemodynamics by inhibiting catecholamine release, blocking catecholamine receptors, and causing vasodilation.[19] In our case, given an anticipated short surgical time (actual time: 42 min) and magnesium's action on enhancing the effect of non-depolarizing muscle relaxants, we considered a single bolus sufficient to avoid unnecessary weakness and prolonged intubation after the surgery.[19] Secondly, although we followed the recommended dosing schedule for metyrosine, studies have administered the drug for longer periods of time (one to three weeks) while measuring urine catecholamines to determine the response.[8,10] Nevertheless, this would have resulted in an extended length of stay and would have put our patient at increased risk for potentially intolerable side effects. Thirdly, we may have considered maintaining our patient's terazosin while administering metyrosine, as studies have shown that this concomitant administration can result in intraoperative outcomes comparable with alpha-1 receptor blockade with phenoxybenzamine alone.[12,13]

Conclusion

Preoperative optimization of PHEO patients has resulted in decreased morbidity and mortality.[5] Historically, phenoxybenzamine has been the mainstay of this approach. Now that phenoxybenzamine is unavailable to Canadian physicians, we must look for safe and effective alternatives. In our patient, metyrosine showed some evidence of reduced catecholamine synthesis preoperatively but proved ineffective in blunting the response to pneumoperitoneum and tumour manipulation. Anesthesiologists with experience preparing PHEO patients for surgery will acknowledge that this process is as much art as science with seldom a "textbook case". Furthemore, with the loss of phenoxybenzamine, the degree of uncertainty in preoperative PHEO management may now have risen.

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Conflicts of interest None declared.

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