Published in final edited form as:

Clin Endocrinol (Oxf). 2016 December ; 85(6): 990–991. doi:10.1111/cen.13234.

Are patients with hormonally functional pheochromocytoma and paraganglioma initially receiving a proper adrenoceptor blockade? A retrospective cohort study

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While we welcome the comments raised by Lentschener et al on our paper “Are patients with hormonally functional pheochromocytoma and paraganglioma (PHAEO/PGL) initially receiving a proper adrenoceptor blockade? A retrospective cohort study”¹, we believe they reflect a traditional, and to a certain degree, superficial understanding of the natural history of PHAEO/PGL, while exclusively focusing the medical and anesthesiological management of these tumours on blood pressure control. However, the goal of medical and anesthesiological management of PHAEO/PGL should be preventing severe catecholamine-induced cardiovascular and other organ-specific complications that could be associated with a significant morbidity and mortality, as clearly expressed in our paper. Unfortunately, optimal control of blood pressure cannot be achieved in these patients under any circumstances.

PHAEOs/PGLs are catecholamine producing tumours – more than 70% secrete catecholamines into circulation². The PHAEOs/PGLs that do not secrete catecholamines into circulation still produce them (truly biochemically silent PHAEOs/PGLs are extremely rare). However, in these tumours, the catecholamines are rapidly metabolized to metanephrines. Yet, upon tumour manipulation, they behave identically to those secreting catecholamines. The concentrations of catecholamines in these tumours are enormous – potentially creating a volcano that can erupt at any time, not only during surgical manipulation of a tumour³. A severe psychological situation, excessive physical activity, certain foods, or various medications, including those used for nausea, depression, allergies, or infection, can precipitate a sudden catecholamine release in any setting, location, or time of day⁴. Often, these tumours can erupt without a trigger. The above scenarios, including direct PHAEO/PGL manipulation, can lead to significant catecholamine release exceeding normal plasma values 1000 times or greater⁵. Furthermore, approximately 20% of patients

do not present with hypertension due to downregulation of adrenoceptors resulting from prolonged elevation of circulating catecholamines. Enormous catecholamine levels during various attacks or “misleading” normotension behind which catecholamine-secreting is waiting to attack, must be carefully addressed and appropriately approached with the current first line of medical care – an adrenoceptor blockade.

Prior to successful PHAEO/PGL surgical resection, there are two, well described, critical periods of catecholamine excess. The first is before operation and calls for preoperative management, and the second is during the operation, which calls for perioperative management. These tightly linked periods are due to a common denominator – catecholamine excess – and are neglected by Lentschener et al.

During the preoperative period, the most devastating complications are often related to a sudden and/or unexpected release, drug-induced, or prolonged high levels of catecholamines leading to cardiovascular catastrophes such as congestive heart failure, cardiac arrest, severe arrhythmia, myocardial infarction, ventricular thrombosis, stroke, and in some cases, death. As earlier described, there are patients who present with these complications, and have no history of hypertension^{6–8}. Furthermore, before medical management is initiated, subclinical cardiomyopathy, constipation, and other organ-specific problems are detected in a significant number of patients with catecholamine-secreting PHAEOs/PGLs^{9, 10}. Although many classes of medications are effective in lowering blood pressure in patients with PHAEOs/PGLs, only an alpha adrenoceptor blockade is shown to reverse cardiomyopathy and help with other organ-specific problems¹⁰. Thus, we consider an alpha adrenoceptor blockade the best, initial medical management for pheochromocytoma. We do not favor one alpha adrenoceptor blocker over another. In our experience, phenoxybenzamine is extremely effective and well tolerated among nearly all patients and is also recommended by the international expert group that presented a US Endocrine Society and other clinical practice guidelines for these tumors^{11, 12}. The authors statement that phenoxybenzamine is no longer recommended in many European countries can be proven false based on recent practice guidelines for these tumors represented and written by European experts¹¹. Viewing the preoperative medical management of these tumors as simply “hypotensive,” misses the greater clinical picture of patients with these tumors and introduces a severe medical error into clinical practice.

During perioperative management, an appropriate alpha (and if necessary beta) adrenoceptor blockade is crucial for better control of blood pressure and heart rate during any operation when, as stated earlier, circulating catecholamine levels could be enormous. Lentschener et al correctly point out that (1) there has not been a prospective study comparing the various preoperative medical management regimens of PHAEO/PGL and (2) that PHEO resection by adrenalectomy has almost no mortality in a recent series, regardless of preoperative management. First, the authors criticize using alpha adrenoceptor blockades preoperatively, but they are not able to provide evidence from randomized clinical trials that are not using such a blockade. We have strong reservations that an Ethics Committee would approve such a trial. Second, the authors omitted the serious fact that there is a morbidity associated with removal of PHAEO/PGL without appropriate therapeutic management. Thus, the use of perioperative mortality as the sole criterion of success for pheochromocytoma management

asks too little from those of us who take care of patients with these tumors. In our extensive clinical experience with PHAEO/PGL, we have witnessed cases where omission of a preoperative alpha blockade led to severe peri- and postoperative complications, causing permanent damage to the patient and a prolonged hospital stay. We also believe that postoperative length of stay, complications, and quality of life are meaningful criteria in the success of PHAEO/PGL medical management. Furthermore, for perioperative management, Lentschener et al suggest that nicardipine, which decreases blood pressure within 1–3 minutes, or urapidil can be used. In many patients, when blood pressure must be controlled immediately (e.g. those with previous history of cardiac disease, brain aneurysm, older patients with diabetes, etc.) the time period of 3 minutes is unacceptable and not recommended. For these patients, 3 minutes can be devastating and can lead to permanent damage due to stroke, cardiac arrhythmia, or other serious problems. Urapidil is not approved for use in the US. Calcium channel blockers can occasionally be given to some patients who are unable to tolerate alpha adrenoceptor blockers. This approach has likewise been well established¹³.

Another important issue in evaluating the success of PHAEO/PGL medical management is the heterogeneity of both the tumor and the patients themselves. A 1.5 cm incidentally identified PHAEO/PGL may be different from a 7 cm tumor, which more often causes cardiac arrest due to high catecholamine levels. Yet, even the size of a tumor can be meaningless since the greatest factor is their real catecholamine production. Furthermore, a 20-year-old, otherwise healthy patient, is obviously different from an 80-year-old patient with multiple comorbidities. The same applies for pregnant women, where a careful medical management plan must be in place. But again, all patients with these tumors have elevated catecholamine levels and should therefore, have an appropriate adrenoceptor blockade.

The recommendations from Lentschener et al only take into account blood pressure control, which may put a patient in double jeopardy. First, due to the lack of appropriate adrenoceptor blockade during the preoperative period, a patient may be harmed or killed due to excessive catecholamine release from the tumor. Second, during the perioperative period, an inadequate adrenoceptor blockade can result in catastrophic consequences related to morbidity of these patients. “Primum non nocere” in the Hippocratic Oath applies here well and it is up to physicians and their patients to accept such a risk based on the simplified view of Lentschener et al¹⁴.

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