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Adrenergic blockade with phenoxybenzamine and propranolol in a cohort of 60 patients undergoing surgery for phaeochromocytoma

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EDITOR:

Phaeochromocytomas are rare adrenal tumours. Intraoperative tumour manipulation can trigger uncontrolled release of large amounts of catecholamines into the systemic circulation, which can cause potentially lethal cardiovascular instability [1]. Medical pre-treatment aims to obtund the consequences of such intraoperative catecholamine release. Phenoxybenzamine is considered by many to be the drug of choice for treating the hyperkinetic, vasoconstrictive, hypovolaemic form of hypertension associated with phaeochromocytomas. However, it is argued that the long duration of action of phenoxybenzamine may lead to refractory hypotension postoperatively once the catecholamine drive from the phaeochromocytoma has been removed, and hence such patients could need several days of support with vasopressor agents. For this reason, it has been suggested that the drug should be stopped for 48 h before surgery, and most centres advocate routine postoperative admission to intensive treatment unit (ITU) [2].

The optimum dose and the duration of preoperative preparation with phenoxybenzamine have been debated. While some consider that 10 days treatment provides adequate α-blockade [1], others found that even higher doses of phenoxybenzamine (median 160 mg day^{-1}) for a median of 3 weeks achieved only a partial adrenergic blockade [3]. This debate is also fuelled by the observation that severe intraoperative hypertension occured in most patients whether or not α-blockade had been instituted [4] and that similar perioperative results could be achieved whether or not patients received preoperative α-antagonists [5]. In an attempt to avoid such problems, others have used doxazosin [6] or calcium channel blockers [7,8] in the preoperative period. It has even been suggested that preoperative blood pressure (BP) control is no longer necessary at all because there are drugs available to correct sudden changes in cardiovascular dynamics in an era when anaesthetic monitoring is highly advanced [9].

This retrospective review of clinical notes analyses the medical pre-treatment and perioperative haemodynamic events in a cohort of 60 consecutive unselected patients (M : F, 21 : 39; age 22–81 yr) with phaeochromocytoma who underwent an adrenalectomy after adrenergic blockade using a standardized protocol between January 1998 and May 2007.

Patients were started on oral phenoxybenzamine as soon as the biochemical diagnosis of phaeochromocytoma was confirmed. The dose of phenoxybenzamine was titrated until normotension was achieved (mean ± SD dose 40 ± 23 mg day^{-1}). β-Blockade with propranolol was then added to control the heart rate (HR). Patients remained on their individualized drug combination for 6–42 weeks (median 14 weeks) while awaiting surgery. Three groups of patients were identified based on whether the daily dose of phenoxybenzamine tolerated was <30 mg ($n = 13$), 30 mg ($n = 25$) or >30 mg ($n = 22$) (Table 1). These increasing doses of phenoxybenzamine paralleled an increase in the highest systolic BP recorded at the time of diagnosis, levels of 24-h urinary normetepinephrine and metepinephrine and dose of propranolol used (Table 1). Despite these trends, none of these differences reached statistical significance with analysis of variance and Kruskal–Wallis tests.

Patients were admitted 4 days prior to the operation for intensification of the α-blockade.

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Table 1. Biochemical, clinical and intraoperative data (mean ± SD (range)) or number of patients.

Phenoxybenzamine dose	$<30\ mg\ day^{-1}$ ($n = 13$)	$=30\ mg\ day^{-1}$ ($n = 25$)	$>30\ mg\ day^{-1}$ ($n = 22$)
Preoperative management			
Normetepinephrine 0–3.0 μmol $24\ h^{-1}$	16.5 ± 15.6 (1.1–49.5)	21.5 ± 19.9 (4.3–71.9)	25.6 ± 22.5 (3.1–87.0)
Metepinephrine 0–14 μmol $24\ h^{-1}$	8.7 ± 9.9 (0.1–33.5)	18.3 ± 24.5 (0.5–83.1)	19.1 ± 18.7 (0.8–56.8)
Blood pressure (BP) at diagnosis (mmHg)	167 ± 40 (120–260)	186 ± 58 (120–350)	190 ± 34 (140–250)
Phenoxybenzamine oral dose (mg)	18 ± 4 (5–20)	30	80 ± 50 (40–240)
Propranolol oral dose ($mg\ day^{-1}$)	110 ± 70 (40–240)	123 ± 47 (60–240)	150 ± 87 (60–360)
BP on admission (mmHg)	139 ± 23 (110–185)	133 ± 20 (88–170)	140 ± 32 (96–190)
Heart rate on admission ($beats\ min^{-1}$)	69 ± 12 (60–96)	74 ± 14 (50–100)	73 ± 19 (50–116)
Propranolol dose on preoperative day (mg)	170 ± 130 (40–480)	182 ± 78 (80–360)	209 ± 128 (60–480)
Intraoperative BP control			
Intraoperative fluid (mL)	2100 ± 775 (1000–3500)	2590 ± 1610 (1000–8000)	2700 ± 750 (1500–4000)
Drugs*			
Sodium nitroprusside, 9.5 (1–42) mg	7	19	18
$MgSO_4$, 6 (2–13) mg	4	12	12
Phentolamine, 7 (1–25) mg	3	15	12
Labetalol, 50 (2–100) mg	3	8	4
Metaraminol, 6 (1–11) mg	2	6	5
Isoprenaline (5–200 μg)	1	1	1

*For each drug, the median (range) or range dose is given in column 1 and the number of cases in which each drug was used in the other columns.

In that time, they were converted from oral to intravenous (i.v.) phenoxybenzamine starting as a once-daily infusion of 50% of their daily oral dose or $0.5\ mg\ kg^{-1}$ (whichever was the greater) and increasing as necessary in order to achieve normotension at rest with postural hypotension. In all, 53 patients needed $0.5\ mg\ kg^{-1}\ day^{-1}$ and 7 patients needed $1\ mg\ kg^{-1}\ day^{-1}$. Oral intake of fluids was encouraged and, if needed, i.v. fluids were used to compensate for the possible increase in intravascular volume. The daily dose of propranolol was increased to a mean ± SD of 185 ± 70 mg (range 40–480 mg) aiming to achieve a slow resting pulse without postural change (Table 1).

On admission to hospital, patients had similar systolic BP (median 130 mmHg) and HR (median 70 $beats\ min^{-1}$). On the morning of the operation patients had similar systolic BP when lying down (124 ± 18, range 65–165 mmHg) and standing (114 ± 18, range 65–150 mmHg) and HR (67 ± 10 $beats\ min^{-1}$, range 50–90 $beats\ min^{-1}$). Patients were anaesthetized by one of two anaesthetists who used a similar anaesthetic technique. All patients had invasive monitoring of radial arterial pressure and central venous pressure (CVP) before induction with fentanyl 3–5 $\mu g\ kg^{-1}$, propofol 1–2 $mg\ kg^{-1}$ and rocuronium $0.5\ mg\ kg^{-1}$. Patients were intubated and ventilated with isoflurane and N_2O in O_2. Further increments of fentanyl were given as required to maintain analgesia (50–600 μg, median 250 μg).

Increments of vasoactive agents were used intraoperatively in 52 patients (Table 1). No antihypertensive treatment was needed once the adrenal vein had been clamped. All patients received i.v. fluid as crystalloid only or crystalloid plus colloid (1000–7000 mL, median 2400 mL). There was no correlation between the preoperative dose of phenoxybenzamine and the volume of fluid given or the dose and variety of vasoactive drugs used intraoperatively (Table 1). Severe intraoperative hypertension (systolic BP > 180 mmHg) was recorded on the anaesthetic charts of 16 patients (26%). All episodes were transient and lasted no more than 5 min. The maximum BP recorded was 230 mmHg. Severe intraoperative hypotension (systolic BP < 80 mmHg) was recorded in 32 patients (52%) and lasted up to 15 min. The lowest BP recorded in these patients was 50 mmHg. There was no correlation between the preoperative dose of phenoxybenzamine and the severity or duration of intraoperative episodes of hyper- or hypotension. Laparoscopic adrenalectomy was undertaken in 54 patients and open adrenalectomy was performed in six patients. The operating time ranged from 55 to 290 min (median 120 min).

Postoperatively, patients remained in the post-anaesthesia care unit for a median time of 150 min (range 60–330 min). Invasive monitoring of arterial BP and CVP was discontinued. Patients were transferred to a general surgical ward once BP had remained stable for 60 min (systolic BP > 100 mmHg) in the absence of vasoactive drugs or

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volume expansion. Only two patients needed to be admitted to the ICU. One of them needed inotropic support and invasive monitoring for 36 h for persistent hypotension and one needed observation of fluid balance following intraoperative haemorrhage and blood transfusion. Postoperative stay was 1–8 days (median 3 days). In that time, all antihypertensive medication was discontinued and patients remained haemodynamically stable (systolic BP > 100 mmHg with good urine output). No patient developed refractory hypotension. There was no perioperative mortality.

Comparison of our data with other studies is hampered by the variety of definitions of intraoperative hypertension (e.g. ⩾170 mmHg, ⩾200 mmHg or using a 20% change from preoperative values) and hypotension (e.g. <80 mmHg or <60 mmHg). In our series, 26% patients experienced BP > 180 mmHg and 52% patients experienced BP < 80 mmHg. These figures compare well with previously published data. For example, in a series of 80 patients treated during a 10-yr period in North Carolina, 53% of patients had intraoperative hypertension (>170 mmHg) and 28% of patients had hypotension (<90 mmHg) [10].

None of our patients experienced sustained hypertension. This compares favourably with data from a large series of 143 patients treated at the Mayo Clinic where 36 had sustained hypertension (>180 mmHg for >10 consecutive minutes) [11]. In our practice, adrenergic blockade is titrated to the clinical end-points of symptomatic postural hypotension and resting bradycardia and patients are encouraged to reach the limit of their ability to tolerate their medication in the days leading to surgery. Despite this, most patients still needed a multimodal pharmacological approach to achieve intraoperative haemodynamic control. This may be a reflection of the fact that the effects of unpredictable intraoperative surges of catecholamines cannot be prevented or controlled by preoperative adrenergic blockade alone. Also, it demonstrates that it is not possible to produce a complete sympathetic block even after long-term phenoxybenzamine pre-treatment because patients retain the capacity for adrenergic responses. This may explain why patients can return to the ward environment safely without the need for routine ITU admission.

These data illustrate that patients undergoing adrenalectomy for phaeochromocytoma have minimal perioperative haemodynamic disturbance following pre-treatment with oral and i.v. phenoxybenzamine in association with propranolol.

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