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Clinical Experience

The Preoperative Management of Phaeochromocytoma

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SUMMARY

Although the preoperative use of alpha-receptor antagonist drugs is generally accepted for patients with phaeochromocytoma, evidence on the most appropriate treatment and its timing is scarce.

In this retrospective study, the effectiveness of the preoperative preparation of fourteen patients who required surgical excision of a phaeochromocytoma was examined in the light of their operative stability. A simple score was developed of blood pressure stability by scoring the need for additional antihypertensive agents intraoperatively before, and blood pressure support after, tumour removal. A higher score indicated greater instability.

Twelve patients received phenoxybenzamine and their stability was superior to the two patients treated with labetalol and with prazosin. There was no correlation between the duration of treatment with phenoxybenzamine and the operative stability (r=0.18 P=0.55 Spearman). The five patients who were treated with phenoxybenzamine for longer than 10 days did not have better perioperative blood pressure stability than the five patients who had treatment for less than a week.

Predictive factors for intra-operative blood pressure stability were also sought. The degree of postural hypotension after treatment with phenoxybenzamine did not predict operative stability (r=–0.31, P=0.33 Spearman). However, the peak total catecholamine level found during surgery correlated quite well with more operative instability (r=0.65, P=0.031, Spearman), suggesting that patients with phaeochromocytomas with high production of catecholamines are more likely to show cardiovascular instability.

Key Words: ANAESTHESIA; ADRENAL: phaeochromocytoma, preparation, management

It is generally agreed that patients who have been diagnosed as having a phaeochromocytoma benefit from the preoperative use of alpha-adrenergic receptor blocking drugs although according to Merin, this has never been tested in a controlled prospective clinical study[1]. Such a study would be difficult, as phaeochromocytomas are such rare tumours that most institutions could not gather sufficient cases. Most commonly, phenoxybenzamine is used for preoperative preparation as it is a non-competitive alpha-adrenoceptor blocker. The non-competitive aspect would seem important as a patient with a phaeochromocytoma can have circulating catecholamine concentrations during surgery which may be over 500 times greater than normal[2] with the maximal concentrations occurring during the handling of the tumour.

The operative management of patients with phaeochromocytoma may be complicated by large and potentially lethal swings in blood pressure, with high peaks during tumour handling and severe hypotension immediately following removal of the tumour[3]. Pre- and intraoperative care thus requires careful pharmacological control. During surgery, attenuation of surges of blood pressure by drugs such as sodium nitroprusside may be needed and once the surgery has removed the source of excessive catecholamines, patients may require support with a noradrenaline infusion to control hypotension.

The major issues in anaesthetic management have been summarized by Pratilas and Pratila[4], Desmonts

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and Marty[5], Hull[6] and Pullerits et al[7]. The assumption underlying the pharmacological management of the blood pressure during surgical removal of phaeochromocytoma is that the swings occur because of the secretion of catecholamines and insufficient blockade to abolish the responses. These swings may also be exacerbated if adequate time has not been allowed to restore the depleted blood volume[6], although research to date has not substantiated the notion of a contracted blood volume in phaeochromocytoma patients[8].

The ideal method and period of perioperative control of blood pressure in phaeochromocytoma has not yet been established. Merin advocated ten to fourteen days treatment but admitted that the optimal duration of preoperative phenoxybenzamine has not been studied[1]. Hull recommended a treatment period of two to four weeks, but did not give any reference, only stating that the time frame used was "from experience"[6].

This series of patients from the Royal Adelaide Hospital was examined retrospectively to see how well blockade had been achieved and whether the degree of blood pressure instability could be related to the duration of the alpha-receptor blockade. In order to do this a simple predictor of intra-operative instability was devised.

METHODS

Fourteen consecutive patients with histologically confirmed phaeochromocytoma were managed surgically at the Royal Adelaide Hospital between December 1980 and January 1993. The characteristics of the 14 patients are summarized in Table 1. The case histories of three of these patients have been reported in detail previously[9]. All patients in this series were managed by the same medical team under DBF and by the same anaesthetist (WJR) and had serial arterial catecholamine assays performed.

TABLE 1
Demographic and therapeutic details of the patients

Patient Number	Sex	Age yr.	Admission Blood Pressure mmHg	α Blocker	Duration Days	β Blocker
1	M	36	170/100	phenoxy	3	atenolol
2	F	15	160/110	phenoxy	4	atenolol
3	F	43	140/90	phenoxy	6	atenolol
4	F	43	150/100	labetalol	12	labetalol
5	F	59	205/105	phenoxy	14	atenolol
6	F	24	150/100	prazosin	8	atenolol
7	M	54	230/100	phenoxy	14	atenolol
8	F	37	150/105	phenoxy	5	atenolol
9	F	55	220/130	phenoxy	7	——
10	F	43	205/105	phenoxy	15	atenolol
11	M	47	240/120	phenoxy	4	metoprolol
12	F	53	190/90	phenoxy	14	atenolol
13	F	46	215/115	phenoxy	9	metoprolol
14	F	37	230/120	phenoxy	8	atenolol

Patients were managed preoperatively with alpha- and beta-adrenoceptor blockade using the agents shown in Table 1. Doses in each patient were increased to produce the lowest preoperative blood pressure and least variability in heart rate which were acceptable to the patient. In all but two patients this was achieved by gradually increasing the dose of phenoxybenzamine until nasal stuffiness and postural hypotension were as much as the patient could tolerate. Phenoxybenzamine was commenced at 10 mg bd, increased to 10 mg tds on day 2 and then dose increments were adjusted on an individual basis. In one patient the dose had to be decreased to 10 mg daily. The highest dose administered was 20 mg tds. The actual duration of alpha blockade varied from three days to fifteen days in this series. Beta-blockade, usually with atenolol, was begun about 24 hours prior to the alpha-blockade as is our usual practice. This attenuates the reflex increase in heart rate which otherwise would occur if phenoxybenzamine were given first.

Anaesthetic premedication was usually with an opioid and an anti-emetic (metoclopramide). Before commencement of anaesthesia, infusions of nitroprusside 0.01% in 5% dextrose and noradrenaline 0.01% in 0.9% saline were prepared. When the patient arrived in the operating room, ECG and direct blood pressure monitoring were established before induction of anaesthesia. If unusually difficult surgery was expected with substantial blood loss, a central venous catheter was also inserted.

Induction was with thiopentone to achieve unconsciousness and then alcuronium 0.3 mg/kg intravenously for relaxation. Cummings et al have previously shown that this drug gives minimal sympathetic stimulation during intubation[10]. Maintenance of anaesthesia was with nitrous oxide and an opioid. In the early cases, high dose opioid was used. More recent cases have been supplemented with enflurane or isoflurane. During surgery, all blood loss was replaced with whole blood or colloid (usually a 5% albumin preparation) as the loss was observed. In patients where a CVP was monitored, the reading was kept within 2 cm H_2O of the reading at the commencement of surgery.

Before excision of the tumour, rises in blood pressure above 180 mmHg systolic were treated with infusion of an antihypertensive agent. In the first few patients this was done with phentolamine but in the later cases with nitroprusside. After excision of the tumour, systolic pressures below 80 mmHg were

treated with colloid fluid expansion, usually 5% albumin but in some, Haemaccel (Hoechst, Marion Roussel), and a noradrenaline infusion was commenced if the blood pressure remained below 70 mmHg systolic after an additional 500 ml of colloid had been administered. The aim was to continue colloid expansion and reduction in the noradrenaline infusion rate without allowing the central venous pressure, where available, to exceed 15 cm H_2O measured at the mid-axillary line.

The perioperative behaviour of the patients' blood pressure was given an "instability" score as shown in Table 2.

TABLE 2
Instability criteria for blood pressure control

Phase	Criterion SBP mmHg	Action	Score
Overall	SBP always <180/- and >70/-	Nil	0
During surgery	SBP >180/-	Given phentolamine or nitroprusside	1
After tumour removal	SBP <70/- after infusion 500 ml colloid	Noradrenaline infusion	2
Postoperative	SBP <70/- requires noradrenaline support for SBP	Continued noradrenaline infusion	3

SBP=Systolic Blood Pressure

Patients who needed no additional pharmacological attenuation of the blood pressure during surgery nor support after the tumour was excised were given an instability score of 0. Patients who required some attenuation of their blood pressure but did not require noradrenaline support after the tumour was excised were scored as 1. Patients requiring both attenuation of their blood pressure and noradrenaline support intra-operatively but who were weaned from their infusion before leaving theatre were scored as 2. A patient requiring attenuation of the blood pressure intraoperatively, noradrenaline support after the tumour was excised, and continued noradrenaline support postoperatively was scored as 3 (very unstable).

Arterial catecholamine sampling was performed before induction, after induction but before intubation, as the tumour was being manipulated before vascular isolation (peak BP) and 5 minutes after the tumour was removed. The arterial samples were stored immediately on ice, the plasma spun off and stored at –20°C. The samples were analysed for adrenaline, noradrenaline, and dopamine by the radioenzymatic method of Da Prada and Zürcher[11].

RESULTS

Instability

No additional pharmacological attenuation of the blood pressure during surgery was needed in three patients. In addition, none of these required support after the tumour was excised. These patients were given an instability score of 0. Six patients required some attenuation of their blood pressure but did not require noradrenaline support after the tumour was excised. These were scored as 1. Four patients required both attenuation of their blood pressure and noradrenaline support intraoperatively but were weaned from their infusion before leaving theatre. These patients were scored as 2. One patient, who received labetalol, required attenuation of the blood pressure intraoperatively, noradrenaline support after the tumour was excised, and continued noradrenaline support postoperatively. This patient was scored as 3 (very unstable).

The preoperative preparation of these patients was examined in the light of their operative instability (Figure 1). There was no relationship between the duration of treatment with phenoxybenzamine and the operative stability score (Spearman rank correlation coefficient=0.18, P=0.55). Short treatments were no worse than the longer ones.

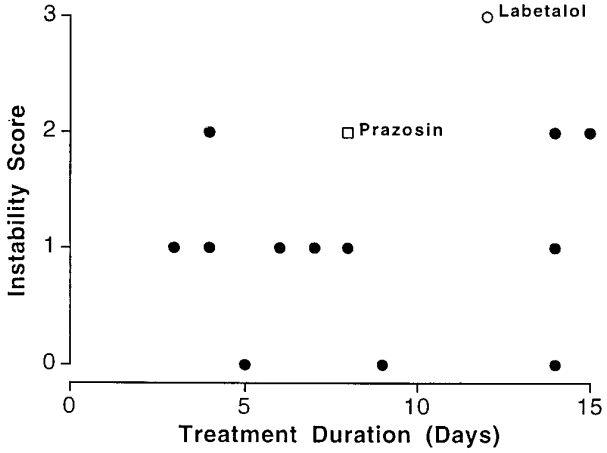

FIGURE 1: Diagram of the duration of treatment and the instability score. The solid dots indicate patients treated with phenoxybenzamine. The patient treated with prazosin for eight days is shown as an open square and labelled as prazosin. The patient given labetalol for 12 days is shown as an open circle and labelled as labetalol. There is no increase in stability with longer treatments.

Similarly, the postural blood pressure response to preoperative treatment was examined as a possible predictor of the stability or instability of the operative course (Figure 2). It can be seen that there is no significant relationship and postural blood pressure change is not a useful predictor of operative stability

(Spearman rank correlation –0.31 $P=0.33$). In addition, the data on the patients treated with phenoxybenzamine were analysed to see if the peak total catecholamine level reached during surgery could be related to the perioperative stability. A good correlation was found between the instability score and the logarithmic peak catecholamine concentration (Spearman rank correlation coefficient=0.65, $P=0.031$, Figure 3)

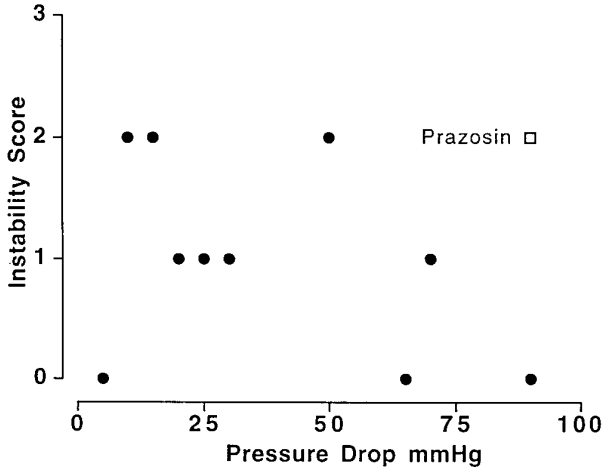

FIGURE 2: Diagram of the systolic pressure drop after preoperative treatment related to the instability score. The solid dots indicate patients treated with phenoxybenzamine. The patient treated with prazosin for eight days is shown as an open square and labelled as prazosin. Postural drop readings were available for only ten of the patients treated with phenoxybenzamine. Preoperative pressure drop does not predict the operative stability.

DISCUSSION

From the two cases in the present study it would appear that treatment with either prazosin or labetalol seems to be less effective than phenoxybenzamine in patients with phaeochromocytoma. Although prazosin has been reported to be effective in some cases, other reports have suggested that its effect is incomplete and less stability is likely during removal of the tumour[12]. Labetalol has been previously reported as unsatisfactory[13]. This is not surprising as both prazosin and labetalol are competitive adrenoceptor blockers and therefore their effect can be overcome by increased agonist levels. In addition, labetalol is a drug with mainly a beta antagonist effect whereas the problem with most phaeochromocytomas appears to be predominantly alpha receptor stimulation. Our series is perhaps slightly unusual in that we commenced beta-blockade just before the alpha block. Although concern has been expressed that this may lead to an excessive initial hypertension, this was not seen with any patient in this series.

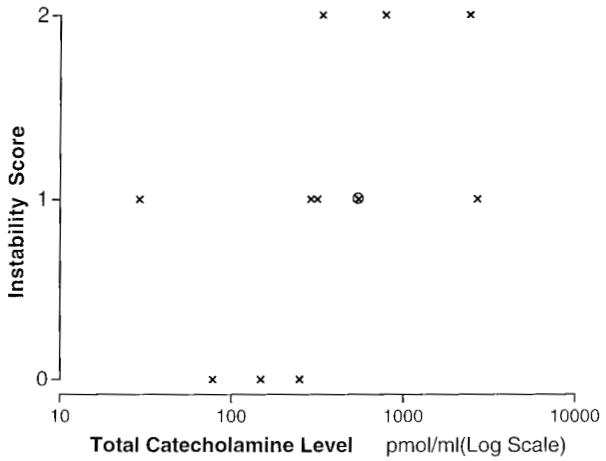

FIGURE 3: Diagram of the peak total catecholamine concentration and the instability score for patients treated with phenoxybenzamine. The circle and cross is the point for two patients with the same instability score and almost the same peak total catecholamines (548 and 550). The total catecholamines are given as a logarithmic scale. There is a good correlation between the score and the logarithmic peak catecholamine concentration (Spearman r=0.65, $P=0.031$).

An assessment of operative stability of blood pressure does not appear to have been performed previously. Although crude, it does provide an estimate of instability and the effectiveness of management in a most important aspect, i.e. that of blood pressure control.

This review goes some way towards answering both Merin and Hull's question of the duration of preoperative treatment. The shortest time of treatment for a patient with excellent stability was five days and even three days gave good stability in one patient.

Although the importance of restoration of circulating blood volume has been suggested by some authors, there is no experimental evidence to support this. The one study we could find did not show any expansion of blood volume occurring with phenoxybenzamine treatment[8]. Certainly whatever the mechanism, our results do not support the need for two to four weeks preoperative treatment sometimes recommended for phenoxybenzamine.

Postural hypotension with treatment has been previously suggested as a good measure of adequate alpha-blockade and attenuated pressure responses to posture have been reported[14]. However in the present series, the postural drop did not correlate with perioperative stability.

Only peak levels of total catecholamines were related to operative stability. If the peak level of catecholamines is a good predictor of instability, then possibly a variable which could be expected to be

associated with the catecholamine surges may be the best guide to the optimal preoperative management. Techniques such as ambulatory blood pressure monitoring are now available and possibly the maximum blood pressure variation over 24 hours would be a good guide. It may be possible to set an upper limit of fluctuation such as 60 or 80 mmHg. Indeed such ambulatory monitoring has already been used to identify that the diurnal rhythm of blood pressure and pulse rate is lost in patients with phaeochromocytomas but restored by alpha blockade[15].

The results of this small series are only tentative as the series is retrospective, but it does give an indication that maximal phenoxybenzamine treatment for as little as three to five days preoperatively is effective in the preoperative management of phaeochromocytoma.

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