Anaesthetic management with morphine in phaeochromocytoma

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Morphine was used as the principal anaesthetic agent for five patients undergoing resection of phaeochromocytoma, and changes in plasma catecholamines were monitored. Phenoxybenzamine ($0.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) was orally given one week before operation. After premedication with hyoscine (0.4 mg) and diazepam (20 mg) of meperidine (50 mg), anaesthesia was induced with an infusion of morphine ($1 \text{ mg} \cdot \text{kg}^{-1}$) over 30 min and maintained with diazepam, nitrous oxide and oxygen. Pancuronium was used as the muscle relaxant. In three of the five patients, blood pressure transiently rose (ranging from 15 to 60 mmHg) following orotracheal intubation, but vasodilators were not required. In two of the three, plasma norepinephrine increases were 1.1 and 1.3 $\text{ng} \cdot \text{mL}^{-1}$. In the other two patients, whose blood pressure was stable, the change in plasma norepinephrine was 0.1 and 0.7 $\text{ng} \cdot \text{mL}^{-1}$. After reaching a peak at the time of ligation of drainage vein from the tumour, plasma catecholamines rapidly decreased to the preoperative levels, but the blood pressure was well maintained in all cases. Ventricular arrhythmias did not occur despite the increased levels of endogenous catecholamines.

These findings suggest that morphine can be used as an alternative anaesthetic agent during operation for phaeochromocytoma and that exaggerated pressor responses to morphine (when given slowly) seem not to occur in phaeochromocytoma.

Key words

ANALGESICS: morphine; SURGERY: phaeochromocytoma.

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Surgical treatment of phaeochromocytoma is much less hazardous with the use of adrenergic receptor blockade, vasodilators and blood volume replacement before operation; however, the choice of anaesthetic agents still remains important. Among the anaesthetic agents currently used, neuroleptoanalgesia and enflurane are most popular. Morphine is rarely used because it is a potential releaser of histamine,^{1,2} which in turn leads to catecholamine release from the sympathetic nerve endings. Indeed, histamine has been used as a provocative test in the diagnosis of phaeochromocytomas, but it is unclear if the endogenous histamine liberated by morphine enhance catecholamine release and provoke a hypertensive attack. Clinical effects of morphine on blood pressure in phaeochromocytoma patients are not consistent; they include prolonged hypertension followed a dose of 10 mg of diamorphine³ while there were no apparent adverse effects in patients given 5 mg of morphine sulfate as premedication.⁴⁻⁷ Furthermore, morphine itself does not significantly depress cardiac function and has remarkable peripheral vasodilating effects which reduce peripheral vascular resistance and increase venous capacitance.⁸⁻¹⁰ In patients with phaeochromocytomas, cardiac function is often impaired because of catecholamine-induced myocardial damage and longstanding pressure overload.^{11,12} Thus, we postulated that, if morphine-induced histamine release was not so extensive as to evoke hypertension, morphine might be an acceptable anaesthetic agent for use during excision of phaeochromocytomas.

Case report

Three patients with unilateral adrenal tumours and the two with bilateral adrenal tumours were studied. Hypertension was paroxysmal in four and sustained in one (Table I). The ECG was abnormal in four of

TABLE 1 Clinical profiles of five cases of pheochromocytoma studied

	<i>Case-1</i>	<i>Case-2</i>	<i>Case-3</i>	<i>Case-4</i>	<i>Case-5</i>
Age and Sex	37 M	33 M	65 F	51 F	44 M
Hypertension	paroxysmal	paroxysmal	paroxysmal	sustained	paroxysmal
Blood pressure (at attack)	125/80 (210/130)	120/80 (220/160)	140/80 (200/120)	160-200/120	150/76 (200/140)
EKG findings	CRBBB	LV strain	LVH	LV strain	normal
Venous level of catecholamines	E: 0.48 NE: 2.1	E: 0.25 NE: 0.50	E: 0.38 NE: 0.17	—	E: 0.4 NE: 1.5

CRBBB: complete right bundle branch block, LVH: left ventricular hypertrophy, E: plasma epinephrine (ng/ml), NE: plasma norepinephrine (ng/ml)

the five and venous levels of catecholamines were increased in three of the four patients studied; epinephrine (E) predominantly increased in one and both epinephrine and norepinephrine (NE) in two. Phenoxybenzamine ($0.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) was given for one week before operation. After premedication with intramuscular hyoscine (0.5 mg) and diazepam (20 mg) or meperidine (50 mg), anaesthesia was induced with a drip infusion of morphine sulfate ($1 \text{ mg} \cdot \text{kg}^{-1}$), over a 30 min period. When half the dose had been given, orotracheal intubation was carried out. Adequate depth of anaesthesia was maintained with diazepam, nitrous oxide and oxygen, and relaxation was obtained with pancuronium bromide. ECG, and arterial and central venous pressures were monitored. Phentolamine, sodium nitroprusside and propranolol were infused as required by fluctuations in blood pressure or by tachycardia.

Blood samples were obtained through an indwelling catheter placed in a peripheral vein before induction of anaesthesia and thereafter from a radial artery. Plasma catecholamine were determined using an automated fluorometric method coupled with liquid chromatography, as previously reported.¹³

Changes in arterial blood pressure and plasma catecholamine are summarized in Table II. During the anaesthetic induction by morphine infusion, blood pressure was stable and there were small increments of plasma catecholamines in two patients (Cases 2 and 4). The former patient was given hydroxyzine (50 mg) with the same premedication as the other patients. In three patients, blood pressure increased concomitantly with orotracheal intubation. The increases of plasma NE were 1.1 and $1.3 \text{ ng} \cdot \text{ml}^{-1}$ in two patients, but in Case 3, the

plasma sample was improperly taken. All these changes were transient and returned to the preoperative levels before the operation started. Adrenergic blockers were not required. Surgical manipulation of the tumour evoked marked fluctuation of blood pressure and considerable changes in plasma catecholamines in all cases. Within 30 min after removal of the tumour, plasma catecholamines rapidly decreased to the preoperative levels and no ventricular arrhythmias appeared, even at the peak of the blood pressure elevations. There were no patients in whom vasopressors were required to prevent circulatory collapse.

The anaesthetic course and changes in plasma catecholamines in Case 1 are briefly described.

Case 1 (Figure): This 37-year-old man had had occasional bouts of hypertension and weight loss of two years duration. Blood pressure ranged from 125/50 to 210/130 mmHg. ECG revealed first degree A-V block and complete right bundle branch block. Peripheral venous level of catecholamines at rest was $0.48 \text{ ng} \cdot \text{ml}^{-1}$ of E and $2.1 \text{ ng} \cdot \text{ml}^{-1}$ of NE. After premedication with intramuscular hyoscine (0.4 mg) and diazepam (20 mg), anaesthesia was induced as described above. Blood pressure increased 15 mmHg and a concomitant elevation of plasma NE was noted at the time of orotracheal intubation. NE levels returned to the preinduction state before the start of operation. Immediately after initiation of surgical manipulation, plasma catecholamine levels abruptly increased and reached a peak of $6.2 \text{ ng} \cdot \text{ml}^{-1}$ of E and $17.2 \text{ ng} \cdot \text{ml}^{-1}$ of NE. Blood pressure fluctuated widely despite phentolamine infusion. Propranolol (1.0 mg) was given at the appearance of tachycardia. After ligation of the drainage vein from the tumour, plasma catecholamines rapidly decreased to the preoperative level

TABLE II Alterations in systemic blood pressure and plasma catecholamines

	Case-1			Case-2			Case-3		
	B.P.	E	NE	B.P.	E	NE	B.P.	E	NE
<i>Anaesthetic Induction</i>									
Before the infusion	100/50	0.34	1.85	150/90	0.54	0.42	160/90	0.38	0.17
After the start of infusion	105/70	0.29	2.02	150/90	0.46	0.81	140/80	0.51	0.28
At orotracheal intubation	120/110	0.21	3.11	145/90	0.26	0.91	200/120	—	—
<i>During the operation</i>									
Peak level	180/110	6.20	17.2	215/100	10.4	23.9	220/110	17.3	2.50
After removal of the tumour	140/90	0.97	1.70	140/80	1.10	2.10	120/75	0.56	0.33
	Case-4			Case-5					
	B.P.	E	NE	B.P.	E	NE			
<i>Anaesthetic Induction</i>									
Before the infusion	130/85	0.30	1.0	130/90	0.44	1.4			
After the start of infusion	155/90	0.50	0.73	145/90	0.44	1.0			
At orotracheal intubation	150/105	0.32	1.43	170/105	0.48	2.3			
<i>During the operation</i>									
Peak level	215/105	14.0	13.0	210/100	1.1	13.6			
After removal of the tumour	150/105	0.62	1.32	160/100	0.7	1.3			

B.P.: arterial blood pressure (mmHg), E: plasma epinephrine, NE: plasma norepinephrine (ng/ml)

while the blood pressure remained elevated before gradually decreasing on the following day. Arrhythmias were absent, even at peak of plasma catecholamines and blood pressure. The ECG was normal postoperatively.

Discussion

The anaesthetic management of patients with phaeochromocytomas remains a challenge for anaesthetists and has been directed toward the preservation of cardiovascular stability and smooth withdrawal from the chronic excess catecholamine state. In addition to preoperative use of adrenergic receptor blockade and expansion of the contracted blood volume, the proper choice of anaesthetic technique minimizes the surgical hazards. A variety of anaesthetic agents have been successfully used.^{7,14} There is no previous report of morphine

anaesthesia for phaeochromocytomas and it had been considered that the use of morphine should be avoided.

In recent years, enflurane has become the agent of choice for phaeochromocytomas,¹⁵⁻¹⁹ since it is less arrhythmogenic²⁰ and is associated with less hypertension.¹⁹ Isoflurane was proposed for patients with phaeochromocytoma and associated cerebral abnormalities or impaired renal function,²¹ since this agent does not produce EEG abnormalities and is metabolized less than enflurane. Methoxyflurane and fluroxene are seldom used, because of the potential for nephrotoxicity (methoxyflurane) and flammability (fluroxene) although these agents are less arrhythmogenic.^{22,23} Halothane depresses the sympathoadrenal system but sensitizes the heart to catecholamines, resulting in a high incidence of arrhythmias.²⁴ Neuroleptoanalgesia, with combination with droperidol and fentanyl,^{6,25}

FIGURE Plasma catecholamines, blood pressure and heart rate during phaeochromocytoma resection in a 37-year-old patient (case 1).

has been used. However, droperidol occasionally produce hypertension in these patients.²⁶

Induction with thiopentone has been most frequent, but is often accompanied by hypertension and increased plasma catecholamines. Of interest is whether or not slow anaesthetic induction may cause less haemodynamic changes than those of rapid induction. We infused morphine slowly, over a period of 30 minutes. Blood pressure was unchanged in two patients, slightly increased in two. In the remaining patient whose blood pressure was moderately increased, the depth of anaesthesia appeared to be insufficient to suppress stimulation of the sympathoadrenal system. Slow induction of anaesthesia by morphine infusion did not produce an exaggerated pressor response in any patient studied and proved to be effective in maintaining cardiovascular stability during the induction.

Little information is available concerning the haemodynamic effects of morphine in patients with phaeochromocytomas. Rosow *et al.* reported a significant rise of plasma histamine levels following $1 \text{ mg} \cdot \text{kg}^{-1}$ of morphine and found that the reduction

of systemic vascular resistance was inversely correlated to plasma histamine in patients undergoing coronary bypass operation.² We infused morphine three times slower than did Rosow, but histamine levels might increase in response to morphine infusion. From our observations in the five patients, it appears the peripheral vasculature may have been insensitive to the vasodilating action of morphine, perhaps due to an increased sympathetic tone. We speculate that unless a large amount of histamine is released by morphine, peripheral vasodilatation might be immediately reversed by reflex stimulation of the sympathetic nervous system. The phenoxylbenzamine given for one week before operation likely attenuated the pressor effect of morphine in our patients. The measurement of plasma histamine will be necessary to clarify the pharmacologic actions of morphine in patients with phaeochromocytomas.

Large changes in plasma catecholamines occurred during the operative manipulation of the tumour, similar to previous reports with other anaesthetic agents.^{6,16,18,27} Unlike the rapid recovery of catecholamines, blood pressure was maintained at high levels for several hours after removal of the tumour. We assume the sympathetic nervous system remains involved in the preservation of blood pressure after tumor removal. However, the pharmacologic effects of morphine are uncertain: some have reported stimulation,^{8,28} while others found reflex reduction of sympathetic discharge following morphine-induced haemodynamic change^{9,10} or postulated specific interaction with an opioid receptor in the brain, resulting in the suppression of sympathetic outflow.²⁹ The direct local action of morphine on the adrenergic receptors in peripheral vasculature is not clear.^{30,31} In addition, supplement such as nitrous oxide and diazepam produce significant obtundation of the sympathetic nervous system and cardiovascular responses, in contrast to the use of morphine alone.³²

Our experience suggests that morphine warrants further consideration as an anaesthetic agent for use during phaeochromocytoma resection, but that further studies are required.

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Résumé

Chez cinq malades, on a effectué une résection d'un phéochromocytome sous anesthésie à la morphine en mesurant, durant l'intervention, les fluctuations des concentrations des catécholamines plasmatiques. Les malades ont été préparés à la phénoxybenzamine ($0.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{jour}^{-1}$) administrée par voie orale dans la semaine précédant l'intervention. A la suite d'une prémédication faite d'hyoscine (0.4 mg) et de diazépam (20 mg) ou de mépéridine (50 mg), on a induit l'anesthésie par une infusion de sulfate de morphine ($1 \text{ mg} \cdot \text{kg}^{-1}$) sur une période de 30 minutes, complétée de diazépam, de protoxyde d'azote, d'oxygène et de bromure de pancuronium. Chez trois de ces cinq malades on a observé une augmentation transitoire de la pression artérielle de 15 à 60 mmHg au moment de l'intubation orotrachéale, mais cette augmentation n'a pas nécessité de vasodilatateurs. Chez deux de ces trois malades, on a observé une augmentation de la norépinéphrine plasmatique de 1.1 et $1.3 \text{ ng} \cdot \text{mL}^{-1}$ respectivement. Chez les deux autres malades dont la pression artérielle est restée stable, les concentrations de norépinéphrine plasmatique étaient respectivement de 0.1 et $0.7 \text{ ng} \cdot \text{mL}^{-1}$. Une fois atteint le pic de concentration des catécholamines plasmatiques au moment de la ligature de la veine drainant la tumeur, les concentrations ont rapidement diminué au niveau préopératoire alors que la pression artérielle demeurait stable en tout temps. Aucune arythmie ventriculaire n'est apparue en dépit de ces variations des catécholamines endogènes. Ces constatations suggèrent que la morphine constitue un agent anesthésique acceptable pour la résection d'un phéochromocytome car les flambées hypertensives en réponse à la morphine administrée lentement ne semblent pas survenir en présence d'un phéochromocytome.