Prevention of Hypertensive Crisis with ATP during Anesthesia for Pheochromcytoma

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In the anesthetic management of five patients undergoing excision of pheochromocytoma, adenosine triphosphate (ATP) was used for the purpose of regulating systemic arterial pressure during the period of tumor manipulation. ATP was administered at doses of 0.05–0.4 mg/kg/min. Systemic arterial pressure showed a significant decrease from 162±17/103±11 mmHg before manipulation to 136±21/81±10 mmHg during the manipulation period. The plasma catecholamine levels showed significant increases in this period. Immediately after excision, the systemic arterial pressure was maintained at normal levels (118±13/75±16 mmHg) by fluid replacement and discontinuation of ATP administration, subsequently becoming 129±19/79±16 mmHg. The heart rate was very stable and tachycardia did not ocurr during the manipulation period. Only one arrhythmic episode ocurred in one patient. The systemic vascular resistance index was significantly lower during the manipulation period than before it. It was therefore considered that ATP was useful as an agent for controlling arterial pressue during the anesthesia for pheochromocytoma. (Key words: ATP, catecholamine, hypertensive crisis, hemodynamics, pheochromocytoma)

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The surgical mortality rate in pheochromocytoma has recently decreased dramatically due to a better understanding of the pathophysiology of this disease and by the use of pharmacological agents with specific agonistic or antagonistic properties[1,2]. Alpha-adrenergic blocking agents such as phentolamine or phenoxybenzamine have been used for treatment of hypertensive crisis, and beta-blocking agents such as propranolol for treatment of tachyarrhythmias[2–4]. However, as several problems have been involved in the use of these drugs, some authors have voiced reservations over their choice[5–7]. Moreover several attempts have been made to use new drugs such as prazocine, labetalol or sodium nitroprusside (SNP) with a view to finding an ideal drug[5].

The prevention of hypertensive crisis is one of the most important problems in the anesthetic management of patients with pheochromocytoma. Adenosine and its derivatives (e.g. adenosine triphosphate, ATP) are known to be potent vasodilators, and used clinically for hypotensive anesthesia in several countries[8,9]. These agents have very rapid onset time and recovery[9,10]. Moreover they have interesting characteristics, namely an anti-arrhythmic effect in epinephrine-treated animals and also the ability to antagonize the effect of epinephrine-induced hemodynamic changes[11–15]. On the basis of these characteristics, this study was performed to use ATP for controlling arterial pressure during anesthesia in patients with pheochromocytoma.

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Patients and Methods

Five patients with a confirmed diagnosis of pheochromocytoma consented to be subjected to this study.

Two of the patients were preoperatively treated with alpha- and beta-blocking drugs with the circulating blood volumes being corrected with blood transfusion. One patient was treated with a calcium channel-blocker. The remaining two patients did not receive any medication as they were suffering from only hypertension and not from severe hypertensive crisis or tachyarrhythmias (table 1). During the anesthesia for excision of pheochromocytoma, 10% ATP solution was injected into a peripheral vein by means of a infusion pump (ATOM, Infusion Pump, Model-201) for the purpose of regulating systemic arterial pressure. Administration of ATP was timed so as to commence with the start of manipulation of the tumor. The initial dose, 0.1 mg/kg/min, was adjusted so that the arterial pressure would show normal levels. Administration was discontinued immediately after ligation of the tumor vessels. Fluid and blood replacement was performed with reference to bleeding volume, urine volume, arterial pressure, heart rate and pulmonary capillary wedge pressure. Five milligrams per kilogram thiopental and inhalation anesthetics were given to produce deep anesthesia and 1–2 mg/kg succinylcholine was used for induction of anesthesia, followed by endotracheal intubation. In order to maintain anesthesia, nitrous oxide (66%) and halothane (1%) were used in three of the patients, and nitrous oxide (66%) and enflurane (2%) were used in the other two. All patients were given neuromuscular blocking drugs (pancuronium bromide or alcuronium chloride), and respiration was adjusted to normocapnea using endtidal CO_2 as a reference (Parkin Elmer MGM 1100). The radial artery was cannulated and direct arterial pressure was monitored and recorded together with the electrocardiogram (Hewlet Packard Model 78342A). A Swan-Ganz thermodilution catheter (Edwards, 93A-131H-7F) was introduced via the internal jugular vein into the pulmonary artery so that cardiac output, pulmonary arterial pressure, pulmonary capillary wedge pressure and right atrial pressure could be monitored.

Table 1. Preoperative urine catecholamines and treatment

		Urine catecholamines μg/day	Preoperative treatment
Patient 1	E	344–386	Diltiazem
	NE	181–186	250 mg/day
Patient 2	E	31–118	Propranolol
	NE	379–1272	60 mg/day
			Prazocin
			4 mg/day
			Blood transfusion
			600 ml
Patient 3	E	100–145	Prazocin
			1 mg/day
			Blood transfusion
			400 ml
Patient 4	NE	76–477	No medication
	E	7.8–11.6	
	NE	93–215	
Patient 5	E	4.3–11.6	No medication
	NE	396–537	

E: Epinephrine, NE: Norepinephrine.
Normal values: E<12.0 μg/day, NE 10–90 μg/day

The course of anesthesia was divided into four periods, i.e., before manipulation (from the start of the operation to the time before manipulation of the tumor), during manipulation (from the start of manipulation to ligation of the tumor vessels), immediately following excision (from ligation to 15 min afterwards) and post excision (from 15 min after ligtation to the end of the operation). Arterial pressure and heart rate were determined every 5 min and means in each of the four periods were calculated. The hemodynamic parameters from the thermodilution catheter were determined once or twice before manipulation, two to five times during manipulation, once immediately after the excision period, and one to five times during the post excision period, with the mean of each parameter

Table 2. Plasma catecholamine levels during anesthesia

		Before anesthesia	After anesthesia	Before manipulation	During manipulation		Immediately after excision	Post excision
Patient 1	E. ng/ml	1.13	1.81	2.33	18.4	17.40	0.69	0.25
	NE.ng/ml	0.82	1.34	1.77	10.8	13.50	0.86	0.62
Patient 2	E. ng/ml	0.55	0.86	0.70	6.61	3.56	0.25	0.09
	NE.ng/ml	8.09	16.40	16.20	91.30	47.50	2.49	0.53
Patient 5	E. ng/ml	0.03	0.11	0.05	0.13	0.09	0.08	0.04
	NE.ng/ml	1.41	4.54	2.51	7.06	30.00	3.40	0.60

E: Epinephrine, NE: Norepinephrine.

being calculated for each four period. Three patients underwent arterial sampling before anesthesia, after anesthesia, before manipulation, during manipulation (from 2 points), immediately following excision of the tumor, and during the post excision period.

All values were expressed as means ±standard deviations. To determine whether the values obtained at each period were significantlly different from those of the previous period, the paired Student's t test was used for comparison. P value of less than 0.05 was considered significant.

Results

The dose of ATP administered was 0.05–0.4 mg/kg/min with the mean time during which ATP was used being 47±18 min. Plasma catecholamine levels increased markedly during the manipulation period in the three patients who underwent blood sampling; the epinephrine and norepinephrine levels were six to tenfold higher than those before manipulation, and rapidly decreased immediately following the excision period (table 2).

The systolic arterial pressure and diastolic pressure were 162±17/103±11 mmHg, 136±21/83±10 mmHg, 118±13/75±16 mmHg and 129± 19/79±16 mmHg before manipulation, during manipulation, immediately following excision and during the post excision period, respectively. The systolic and diastolic arterial pressures during the manipulation period were significantly lower than those before manipulation, and the systolic arterial pressure immediately following excision was lower than that during manipulation but maintained normal levels (table 3, 4). No vasopressors such as norepinephrine were used.

The heart rates were 103±18 beats/min, 101±18, 99±13, 93±10 before manipulation, during manipulation, immediately following excision and during post excision, respectively. No significant changes occurred in heart rate during manipulation, compared with before the manipulation period (table 3). One episode of ventricular arrythmias was observed during the manipulation period in one patient (patient 3), but it was successfully treated with the use of 0.5 mg propranolol. The remaining four patients were free of arrhythmias.

The systemic vascular resistance index was significantly lower during the manipulation period than before it, i.e., 3045±922 dynes·sec·cm^5/m^2 before manipulation and 2231±808 dynes·sec·cm^5/m^2 during the manipulation period (table 4).

Discussion

Phentolamine has been the drug most commonly used for controlling hypertensive crisis because of the specificity of its alpha-adrenergic blocking action[2]. However, some authors have claimed that phentolamine has too long an onset time and duration of action, and have recommended SNP in preference since its onset of action and recovery are immediate[5]. Phentolamine is believed to have a tendency to act beyond the observed hypertensive period or to induce hypotension immediately after

Table 3. Arterial pressure and heart rate during anesthesia

	Before manipulation		During manipulation		Immediately after excision		Post excision	
	AP systolic / diastolic	HR	AP systolic / diastolic	HR	AP systolic / diastolic	HR	AP systolic / diastolic	HR
Patient 1	188±18 / 104±13	89±16	172±26 / 94±13	81±6	137±8 / 87±4	93±2	152±9 / 93±4	91±2
Patient 2	162±8 / 101±3	92±2	130±21 / 86±12	95±3	109±3 / 76±1	98±0	114±8 / 75±2	89±3
Patient 3	142±11 / 85±4	115±10	117±24 / 67±14	105±8	112±4 / 65±4	85±1	125±9 / 69±10	85±0
Patient 4	159±15 / 112±14	129±2	130±9 / 85±10	128±3	126±6 / 93±4	120±3	145±16 / 98±9	110±1
Patient 5	159±15 / 112±14	91±2	129±9 / 83±9	94±3	105±16 / 55±10	98±0	109±9 / 60±6	91±1

Values are means±S.D. Calculated every 5 min in each of the patients
Abbreviations used are: AP, arterial pressure (mmHg); HR, heart rate (beats/min)

Table 4. Hemodynamic characteristics during anesthesia

	Before manipulation	During manipulation	Immediately after excision	Post excision
AP systolic	162±17	136±21*	118±13*	129±19*
diastolic	103±11	83±10*	75±16	79±16*
HR	103±18	101±18	99±13	93±10
CI	3.16±0.67	3.60±1.01	3.62±0.95	3.98±1.06
PAm	20±4	17±4	19±6	17±8
PCWP	15±5	12±5	14±7	11±6
CVP	9±2	8±3	7±2	7±4
SVRI	3045±922	2231±808*	2437±1195	2065±821
PVRI	133±110	138±103	129±85	97±49
LVSWI	48±9	46±11	52±11	49±8

*$P<0.05$ as compared to previous values
Values are means±S.D., Abbreviations used are: AP, arterial pressure (mmHg); HR, heart rate (beats/min); CI, cardiac index ($l/min/m^2$); PAm, mean pulmonary arterial pressure (mmHg); PCWP, pulmonary capillary wedge pressure (mmHg); CVP, central venous pressure (mmHg); SVRI, systemic vascular resistance index ($dynes \cdot sec \cdot cm^5/m^2$); PVRI, pulmonary vascular resistance index ($dynes \cdot sec \cdot cm^5/m^2$); LVSWI, left ventricular stroke work index (gm/m^2).

excision period. It is sometimes difficult to control the blood pressure in hypertensive crisis with phentolamine since it does not exhibit a complete alpha-adrenergic blocking effect. Hence, it is used in quantities exceeding a reasonable dose[5,6].

SNP is an extremely short-acting antihypertensive agent, the effects of which cease 60–120 seconds after the infusion is stopped. It has been used to achieve satisfactory results by several investigators and is particularly applicable during the resection of pheochromocytoma. Blood pressure can be kept within normal limits during the manipulation period. However, it is potentially toxic since in high dosages, the

normal metabolic pathways may become overloaded. Free cyanide is then formed, which is able to destroy cytochromes[2,7].

Adenosine and its derivatives (e.g. ATP), known to be potent vasodilators are used clinically for hypotensive anesthesia. These agents produce a rapid drop in blood pressure after administration and a rapid recovery after discontinuation, with the blood pressure being very stable during the hypotensive state[8–10]. This is believed to be due to the short plasma half life of adenosine. Hypotension is produced by a marked decrease in systemic vascular resistance. The half-life of epinephrine and norepinephrine in the blood is extremely short and their release during the surgical management of pheocromocytoma is episodic in nature. Therefore it is considered that ATP is very suitable for management of pheochromocytoma.

The results of this study indicate that ATP could control blood pressure during the manipulation period. The dose of ATP used for hypotensive anesthesia in human patients is 0.2–0.6 mg/kg/min which is not so different from the amounts of ATP used (0.05–0.4 mg/kg/min) for pheochromocytoma in this study.

Arterial hypotension is common after excision of the tumor because of a sudden decrease in plasma catecholamine concentrations. Replacement of blood volume with careful cardiovascular monitoring is now recognized as the treatment of choice for this situation[5]. The results also show that severe hypotension did not occur immediately after the excision period in all cases (table 3). This may be due to the short acting characteristics of this drug and fluid and blood replacement with reference to hemodynamic parameters.

The results of some other experiments have aroused our interest. Sohn et al. reported that ATP has not only an anti-arrhythmic effect but also antagonizes epinephrine-induced increase in heart rate, systemic vascular resistance and arterial pressure[12]. Schrader et al. have reported that adenosine inhbits the inotropic and metabolic effects of catecholamine on isolated guinea pig heart, demonstrating that adenosine inhibited the catecholamine-induced increase of dp/dt and the isoproterenol-induced initial rise in myocardial levels of cyclic 3'5'-AMP, glucose-1-phosphate and glucose-6-phosphate[14]. However, Sohn reported that ATP had no significant effect on epinephrine-induced increases in myocardial contractility. Several investigators observed that ATP inhibits noradrenaline release in blood vessels or other organs and also inhibits the action of epinephrine on vascular smooth muscles in experimental animals[11,13,15,16].

Desmonts et al. presented review of one hundred and two cases of pheochromocytoma who underwent treatment between 1964 and 1976. Anesthetic techniques employed were balanced anesthesia with thiopentone and narcotics (14 cases), halothane (50 cases) and neuroleptanesthesia with droperidol and phenoperidine (38 cases). Phentolamine, trimetaphan or SNP were used as antihypertensive agents. None of the patients received preoperatively adrenergic blocking agents. They reported that during the operation, 55 patients suffered from tachycardia (>150 beats/min), 44 from multiple ectopic ventricular beats or bigeminal rhythm, and 4 from cardiac arrest.

In our study the heart rate was observed to be very stable and tachycardia did not occur during the manipulation period. There was only one arrhythmic episode. These versults may have been due to the anti-arrhythmic property of ATP and its effect to antagonize epinephrine-induced cardiovascular changes.

ATP was able to control well the arterial pressure during anesthesia for pheochromocytoma. It is considered that ATP is a useful drug because of its potent vasodilating action, rapid onset and recovery, and possible anti-arrhythmic, antagonizing effects on the catecholamine-induced cardiovascular changes.

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