SHORT REPORTS

Treatment of dissecting aortic aneurysm and renin-induced hypertension with sodium nitroprusside

Dissecting aortic aneurysm can be managed medically or surgically. Essentially medical treatment consists of lowering systemic blood pressure to reduce the risk of progression of the lesion.¹ We report a patient with dissecting aneurysm treated medically in whom control of blood pressure was made particularly difficult by the development of an ischaemic kidney. The flexibility and potency of sodium nitroprusside considerably simplified management and contributed to a successful outcome.

Case report

A 51-year-old man presented with a history of acute chest pain followed by pain in his loins and left leg. He had no medical history of note, and was not known to be hypertensive. Relevant findings at this time were a cold, pulseless left leg, a blood pressure of 160/90 mm Hg, and a normal ECG and chest x-ray film. Dissecting aortic aneurysm was diagnosed and he was transferred to the intensive care unit. Infusion of sodium nitroprusside was started while directly monitoring systemic blood pressure. Propranolol and alpha-methyldopa were also administered by mouth, the systolic blood pressure being maintained between 90 and 100 mm Hg. Aortic angiography, performed 12 hours after admission, showed a type III dissection, with complete occlusion of the left common iliac artery and negligible filling of the left renal artery. A re-entry site was not demonstrated.

Perfusion of the left leg improved over the next few days, and eventually all pulses returned. After seven days of treatment with sodium nitroprusside we decided to change completely to oral antihypertensives. Hydralazine and labetalol were added to the alpha-methyldopa and propranolol, followed by phenoxybenzamine and intravenous labetalol. Nevertheless, satisfactory control could not be achieved and the infusion was started again. This was immediately successful in lowering the patient's blood pressure. It was suspected that an ischaemic left kidney was responsible for the resistance to oral medication, and raised plasma renin concentrations confirmed this (table). It was therefore decided to remove the kidney. All oral antihypertensives were stopped 48 hours before surgery, and the nitroprusside infusion rate was increased. A small, pale left kidney was removed, and despite only minimal blood loss the patient's blood pressure fell dramatically. The infusion was discontinued, and packed cells and plasma were transfused. Twenty-four hours later the blood pressure and plasma renin concentrations had returned to normal, and the patient was returned to the general ward.

The patient had spent a total of 22 days in the intensive care unit and received 2638 mg of sodium nitroprusside during this time. Acid-base estimations were made twice daily, but at no time did he develop a metabolic acidosis. Neither plasma cyanide nor thiocyanate concentrations, monitored daily, ever reached toxic levels (highest cyanide concentration 0.88 $\mu\text{mol/l}$; highest thiocyanate concentration 880 $\mu\text{mol/l}$). Thyroid function was found to be normal.

Plasma renin concentrations (IU/l) in venous blood

Vessel	Preoperative	Postoperative	
		Day 1	Day 2
Left renal vein...	50 000		
Inferior vena cava	9000	600	300

Comment

Sodium nitroprusside is an extremely potent, evanescent hypotensive agent, and these properties made it particularly useful in this case. Its superiority over all the other drugs which were tried was clearly shown, particularly when the patient's blood pressure fell post-operatively: stopping the infusion resulted in a cessation of the depressor effect within five minutes. Some caution must, however, be exercised when using this drug. Overdosage may lead to metabolic acidosis and accumulation of cyanide,² and long-term use may result in a raised plasma thiocyanate concentration, which may suppress thyroid function.³ Acid-base balance, plasma thiocyanate, and thyroid

function must therefore be monitored when infusing sodium nitroprusside over a prolonged period. Despite these qualifications, we consider it to be the drug of choice for this particular clinical problem.

We thank Professor G W Taylor and Mr J S P Lumley for permission to report this case and Mr C J Vesey for his technical help.

¹ Kolff, J, et al, *American Journal of Cardiology*, 1977, **39**, 727.

² Vesey, C J, Cole, P V, and Simpson, P J, *British Journal of Anaesthesia*, 1976, **48**, 651.

³ Nourok, D S, et al, *American Journal of Medical Science*, 1964, **248**, 129.

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Pulmonary oedema associated with ritodrine infusion and betamethasone administration in premature labour

Intravenous administration of beta-sympathomimetic drugs is now the treatment of choice for suppressing premature uterine contractions. Betamethasone or dexamethasone have been used in combination with a beta-sympathomimetic for stimulating fetal lung maturity and preventing respiratory distress.¹

It has been suggested that the combination of these drugs may be responsible for maternal pulmonary oedema²; fenoterol, a beta-sympathomimetic widely used in Germany, has been particularly implicated. We report the case of a patient who received a ritodrine infusion plus betamethasone who developed pulmonary oedema and signs of right-sided heart failure.

Case report

The patient was aged 31 and in her second pregnancy. The first pregnancy four years earlier had resulted in premature labour at 36 weeks' gestation, a healthy 2530-g baby boy being delivered with Simpson's forceps. After this she suffered from secondary subfertility, becoming pregnant after induction of ovulation with clomiphene citrate. There was no evidence of cardiovascular or respiratory disease, although for nine months before this pregnancy she had taken Moduretic (amiloride hydrochloride and hydrochlorothiazide) for occasional ankle swelling. This treatment was discontinued at the start of the pregnancy.

At 19 weeks' gestation a twin pregnancy was confirmed. At 27 weeks' gestation the internal os was found to be one centimetre dilated, and so the patient was admitted to hospital. Three weeks later she had started to have painful contractions. Vaginal examination showed the cervix to be completely effaced and two centimetres dilated. It was decided to start the patient on an intravenous infusion of ritodrine in saline through an IVAC pump and betamethasone sodium phosphate, 8 mg by intramuscular injection twice daily for 48 hours. The dose of ritodrine administered was 50-75 $\mu\text{g/min}$ over 72 hours. The maximum volume of intravenous fluid infused in 24 hours was 750 ml. The patient was allowed free fluids by mouth and had an oral intake of 1900 ml on the day when she started to have dyspnoea. On that day her urinary output was 1100 ml. She subsequently developed progressive dyspnoea with signs of gross pulmonary oedema and right-sided heart failure.

The intravenous infusion of ritodrine was discontinued, and she was placed in an erect position and given frusemide, 40 mg intravenously. The frusemide dosage was repeated two hours later. A diuresis of 5.4 l occurred within five hours and she improved considerably.

Oral ritodrine, 10 mg every four hours, was continued. Sixty hours later progressive premature labour became established and she was delivered of twins at 30 weeks' gestation. Both twins were managed initially in the special care unit but were discharged home aged 13 weeks. The patient has

been followed up for 10 months by PJH. There is no clinical evidence of cardiovascular disease or renal impairment. The chest x-ray film and electrocardiograph are both normal.

Comment

It appears that as a result of the administration of betamethasone together with a low-dose ritodrine infusion this patient developed fluid retention with pulmonary oedema and right-sided cardiac failure. It has been suggested that patients developing pulmonary oedema while taking fenoterol may have an underlying cardiac lesion, particularly an obstructive cardiomyopathy, which would be aggravated by beta-sympathomimetic drugs.² Patients to be subjected to a combination of glucocorticoids plus sympathomimetic drugs should be screened for cardiac lesions before treatment. In those undergoing treatment a careful watch for fluid retention and cardiorespiratory symptoms should be maintained.

¹ Liggins, G C, and Howie, R N, *Pediatrics*, 1972, **50**, 515.

² Kubli, F, *Proceedings of the Study Group on Pre-Term Labour*, Royal College of Obstetricians and Gynaecologists, October 1977, p 218. London, RCOG, 1978.

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Does labetalol increase excretion of urinary catecholamines?

Labetalol has recently been introduced as an antihypertensive drug. Its pharmacological properties include antagonism of both α - and β -adrenergic receptors. Recently it has been reported that labetalol increases excretion of urinary catecholamines¹ and their *o*-methylated metabolites metanephrine and normetanephrine, although urinary excretion of vanillyl mandelic acid (VMA, 4-hydroxy-3-methoxy mandelic acid) was not raised.² The increases were well into the range reported in phaeochromocytoma and one patient underwent an extensive negative exploratory operation.¹

α -Adrenoceptor antagonists can increase the overflow of noradrenaline into the plasma by several mechanisms, including blockade of reuptake of catecholamines, interaction with presynaptic regulatory receptors, and a baroreflex response to the fall in blood pressure. We have examined catecholamine excretion in patients taking labetalol using non-specific spectrophotometric and fluorimetric methods, and have compared the results with recently developed specific radioenzymatic techniques.

Patients, methods, and results

Ten hypertensive patients (age 30-67) taking labetalol 1000-4800 mg daily for 1-27 months were studied. A 24-hour urine collection was made and venous blood sampled after rest in the supine position. Aliquots of urine were analysed for unconjugated noradrenaline and adrenaline using both fluorimetric methods³ and specific radioenzymatic techniques.^{4,5} Total metanephrine and VMA concentrations were measured using spectrophotometric methods. Plasma noradrenaline concentration was measured by a radioenzymatic assay.⁴

Supine plasma noradrenaline concentrations were within normal limits for our laboratory (2.89 ± 0.76 nmol (488 ± 128 ng)). Urinary free catecholamines (noradrenaline and adrenaline) concentrations were grossly raised when measured fluorimetrically (table). When urinary catecholamines were determined by radioenzymatic assay using catechol-*o*-methyl transferase (COMT) without separation of *o*-methylated derivatives, the concentrations were still increased, although lower than those obtained by fluorimetry. Mean noradrenaline and adrenaline concentrations measured by differential fluorimetry were 106 and 351 nmol/mmol creatinine (158 and 566 μ g/g

creatinine) respectively. When the amines were determined by radioenzymatic assay using COMT, with separation by thin-layer chromatography, noradrenaline excretion was 21 ± 3 nmol/mmol creatinine (31.3 ± 4.5 μ g/g), and adrenaline 10 ± 2 nmol/mmol creatinine (16.1 ± 3.2 μ g/g). The results of the COMT assay are within the normal range (table). Urinary noradrenaline determined by a different radioenzymatic method (PNMT-based assay) was similar to the COMT result (table).

Total metanephrines were grossly raised in eight out of the ten cases, and blanks were high with an unusual brown colour. VMA excretion, however, was normal (table).

There was no relationship between apparent amounts of catecholamines or metabolites in urine, determined by non-specific methods, and the dose of labetalol taken.

Urinary noradrenaline and adrenaline (measured by fluorimetric and radioenzymatic methods), metanephrines and vanillyl mandelic acid (measured spectrophotometrically) in ten patients taking labetalol

Case No	Fluorimetric assay NA + A (nmol/mmol creatinine)	COMT assay NA A (nmol/mmol creatinine)	PNMT assay NA (nmol/mmol creatinine)	Total metanephrines (nmol/mmol creatinine)	VMA (μ mol/mmol creatinine)
1	622	21 8	15	232	1.6
2	2931	27 -	17	1999	2.1
3	3934	21 7	11	3012	1.3
4	3266	29 19	20	1466	2.0
5	2174	17 20	23	1596	2.1
6	927	12 11	9	309	1.4
7	2456	18 3	7	1282	1.6
8	2112	10 8	19	917	2.1
9	1525	18 9	15	2471	0.9
10	3930	17 12	39	4650	1.5
Normal range	<50	<50 <20	<50	<650	<3.0

NA = Noradrenaline. A = Adrenaline.

Conversion: SI to traditional units—NA and NA + A: 1 nmol/mmol creatinine $\approx$ 1.49 μ g/g creatinine. A and metanephrines: 1 nmol/mmol creatinine $\approx$ 1.61 μ g/g creatinine. VMA: 1 μ mol/mmol creatinine $\approx$ 1.67 mg/g creatinine.

Comment

The results of these studies using sensitive and specific radioenzymatic methods clearly show that treatment with labetalol does not substantially increase either plasma noradrenaline or the urinary excretion of endogenous noradrenaline or adrenaline. Nevertheless, there is an apparent gross increase in urinary catecholamines and metanephrines, the most likely explanation being that a metabolite (or metabolites) of labetalol interferes with the fluorimetric and spectrophotometric methods. Neither labetalol nor its known metabolites inhibit the activity of either COMT or PNMT and the internal standards used in the assays would take any such action into account. The results of these studies confirm that fluorimetric measurements of catecholamines and metanephrines are unsuitable in patients taking labetalol—and that in these patients urinary VMA should be measured as the screening test for exclusion of phaeochromocytoma. In cases when the VMA is raised, urinary or plasma catecholamines should be measured by radioenzymatic methods.

It is important that clinicians should be aware of the problem of factitious rises of urinary catecholamines in patients taking labetalol. In any case of suspected phaeochromocytoma, further preoperative confirmation of the presence and exact site of the tumour is mandatory.

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¹ Harris, D, and Richards, D A, *British Medical Journal*, 1977, **4**, 1673.

² Chapman, B P, Veitch, A G, and Shephert, B, *British Medical Journal*, 1978, **1**, 364.

³ Von Euler, V S, and Lishajko, F, *Acta Physiologica Scandinavica*, 1961, **51**, 348.

⁴ Henry, D P, *et al*, *Life Sciences*, 1975, **16**, 378.

⁵ Da Prada, M, and Zurcher, G, *Life Sciences*, 1976, **19**, 1161.

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