

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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Department of Obstetrics and Gynaecology, University of Liverpool, Liverpool L69 3BX.

H R ELLIOTT, MRCOG, lecturer in obstetrics and gynaecology

U ABDULLA, MRCOG, senior lecturer and consultant obstetrician and gynaecologist

David Lewis Northern Hospital, Liverpool

P J HAYES, MB, MRCP, senior medical registrar

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)
		NA	A			
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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Department of Clinical Pharmacology, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 0HS

C A HAMILTON, PHD, senior research officer

D H JONES, MSc, MRCP, clinical research fellow and honorary registrar

H J DARGIE, MB, MRCP, senior registrar

J L REID, DM, MRCP, reader and consultant physician