

since adequate respiration took several days to return, respiration was supported artificially. Hypertension and tachycardia did not recur. Recovery was gradual but uneventful. He was discharged 35 days after admission.

Comment

Labetalol was effective in controlling the circulatory effects of adrenergic stimulation from tetanus in this patient, and may be more advantageous than other forms of management using either alpha- or beta-adrenergic blocking drugs. Continuous infusion, although expensive, ensures a reasonably sustained effect and offers a practical alternative to intermittent intravenous or oral administration. Nevertheless, decurarisation should be performed cautiously and adequate doses of atropine must be given. This regimen merits further study.

¹ Stoddard, J C, *Intensive Therapy*. Oxford, Blackwell, 1975.

² Keilty, S R, *et al*, *Lancet*, 1968, **2**, 195.

³ Benedict, C R, and Kerr, J H, *British Medical Journal*, 1977, **2**, 806.

⁴ *British Journal of Clinical Pharmacology*, 1976, **3**, suppl No 3, p 681.

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Failure of labetalol to prevent hypertension due to clonidine withdrawal

Abrupt withdrawal of clonidine treatment may be complicated by a severe rebound rise in blood pressure accompanied by symptoms of sympathetic overactivity, severe headache, and increased circulating catecholamine concentrations.^{1 2} The rise in blood pressure usually occurs within 24-48 hours after withdrawing the drug³ but may be delayed for up to 14 days.⁴ Blood-pressure control and reversal of the symptoms may be achieved by reintroducing clonidine or giving α -adrenoceptor-blocking agents. Although symptoms may be abolished by beta-blockers, rebound hypertension may be potentiated because of unopposed sympathetic vasoconstriction.^{2 3} The use of labetalol, a compound that antagonises both α - and β -adrenoceptors, has been proposed for treating clonidine withdrawal and other hypertensive conditions characterised by increased sympathetic activity.^{3 5} We report on a patient in whom severe rebound hypertension developed during gradual clonidine withdrawal and concurrent labetalol treatment.

Case report

A 41-year-old woman with a history of pyelonephritis and analgesic abuse had had high blood pressure for about eight years. Adequate control had been achieved by her general practitioner with clonidine 150 μ g three times daily. She reported that she became "agitated" when she missed or delayed taking her tablets. She presented to hospital with a severe headache and impaired consciousness after having had no clonidine for 22 hours. She was restless, and her blood pressure was 300+/145 mm Hg and pulse rate 55 beats/min. Ocular fundi showed papilloedema with haemorrhages and exudates. The lower limbs were extended, muscle tone increased, and tendon reflexes exaggerated with extensor plantar responses. Hypertensive encephalopathy was diagnosed. An immediate attempt was made to reduce the blood pressure initially with intravenous diazoxide and, when this proved unsuccessful, with nitroprusside infusion. Satisfactory blood-pressure control was subsequently maintained by reintroducing clonidine 150 μ g three times daily. After discharge blood-pressure control deteriorated and labetalol 100 mg three times daily was added. Good control was achieved with this combination, though moderate postural hypotension occurred.

Gradual withdrawal of the clonidine treatment was attempted, beginning at the rate of 150 μ g every five days. When the patient was reviewed after taking the last dose of clonidine she felt well and her blood pressure was well controlled. Labetalol was continued at the same dose. Three days later, however, she presented again to hospital complaining of severe headache and restlessness. Her blood pressure was 230/170 mm Hg. No neurological abnormalities were present. After intravenous diazoxide was given the pressure remained raised at 230/130 mm Hg. Oral clonidine was then

restarted. After four hours the blood pressure was 136/96 and after six hours 110/86 mm Hg. It was considered unwise to attempt to withdraw clonidine again, and the patient was discharged on this drug with good blood-pressure control.

Comment

This case report shows that the hypertensive crisis precipitated by withdrawing clonidine may not be prevented by gradual withdrawal and concurrent administration of labetalol. Interestingly, rebound hypertension was delayed until the last, small dose was stopped. Perhaps further stepwise reduction using 25- μ g tablets (Dixarit) would have been preferable.

The effectiveness of intravenous labetalol as emergency treatment has been documented^{3 5} but experience with oral administration is limited. Larger doses of labetalol might have been more protective. These were not given in this case because of the degree of blood-pressure reduction achieved and the postural effects already present. Because only partial α -antagonism is attained with labetalol, breakthrough may occur when the catecholamine response is excessive. Under these circumstances the vasoconstrictor effect is likely to be augmented by the more potent beta-blocking action of the drug. Further experience is needed before oral labetalol may be recommended for use in patients in whom clonidine is to be discontinued.

¹ Hunyor, S N, *et al*, *British Medical Journal*, 1973, **2**, 209.

² Bailey, R R, and Neale, T J, *British Medical Journal*, 1976, **1**, 942.

³ Reid, J L, *et al*, *Lancet*, 1977, **1**, 1171.

⁴ Vanholder, R, *et al*, *British Medical Journal*, 1977, **1**, 1138.

⁵ Agabiti Rosei, E, *et al*, *British Journal of Clinical Pharmacology*, 1976 (Supplement), **3**, 809.

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Antiplasmin concentrations after surgery: failure of alpha₂-antiplasmin to rise in patients with venous thrombosis

The antiproteases α_2 -macroglobulin, α_1 -antitrypsin, C1 inactivator, and antithrombin III all show antiplasmin activity. Recently a new fast-acting antiplasmin, α_2 -antiplasmin, has been recognised as the major fast-acting antiplasmin.¹ Impaired fibrinolytic activity has been noted after operation in patients who develop deep vein thrombosis (DVT)² so that increased antiplasmin concentrations might be expected in such patients. We have therefore measured concentrations of the three major antiplasmins— α_2 -antiplasmin, α_2 -macroglobulin, and α_1 -antitrypsin—in ten patients who developed positive ¹²⁵I-fibrinogen scans after major surgery and 15 patients with negative scans.

Patients, methods, and results

Plasma was collected half an hour before surgery and on the first and second days after operation from 25 patients undergoing major gynaecological surgery in a clinical trial evaluating anticoagulant prophylaxis.³ Twenty patients were initially studied: 11 were receiving subcutaneous low-dose heparin 5000 units twice daily and nine were receiving subcutaneous saline as a placebo. Patients were screened for the development of deep vein thrombosis by scanning daily with ¹²⁵I-fibrinogen scan for one week. α_2 -Antiplasmin, α_2 -macroglobulin, and α_1 -antitrypsin concentrations were measured by rocket immunoelectrophoresis using specific antisera (α_2 -antiplasmin antiserum was kindly donated by D Collen, University of Leuven). Five of these original 20 patients showed positive scans (three patients on saline and two on heparin). Five further patients who had isotopic DVT were included in the study and all five were in the saline group.