SHORT REPORTS

Paradoxical rise in blood pressure during propranolol treatment

Common side effects of beta-blocking agents include nausea, vomiting, diarrhoea, ataxia, and psychosis. We record another, potentially life-threatening reaction—namely, hypertension—which may be reversed by alpha-adrenergic-blocking agents.

Patients, methods, and results

With the informed consent of relatives 44 patients mainly with acute exacerbations of schizophrenic disorders, in the manic phase of manic-depressive illnesses, or with post-partum psychoses were given propranolol by mouth in rapidly increasing doses. All were taking part in an open trial of the effects of large doses of propranolol.^{1 2} Only two were aged over 45 and none had organic disease. For at least one week before the study all treatment was stopped. The effects of propranolol were monitored by measuring pulse rate and blood pressure every one to three hours.

Most patients received about 600 mg propranolol the first day, the dose being increased by 400-800 mg daily until the pulse fell to 58-64/min, blood pressure falling to about 90/60 mm Hg. The largest individual doses ranged from 600 to 5000 mg daily. When treatment was successful the symptoms improved with the reduction in pulse rate and blood pressure.

The common side effects occurred in a few patients, but eight developed an appreciable increase in blood pressure (table). This was not due to an "escape" from beta-adrenergic blockade because the pulse rate remained low (58-62/min). In most cases the increase was progressive over 3-24 hours, while in two it occurred abruptly, accompanied by other signs of crisis. Two patients developed hypertension when the pulse rate had fallen to about 60/min, and in the others it occurred when the dosage was increased after a reduction had caused partial or complete release of the blockade.

Increase in blood pressure during propranolol treatment

Case No	Sex	Age (years)	Daily propranolol dosage at time of hypertension (mg)	Increase in blood pressure (mm Hg)
1*	F	17	5000	90/60-260/170
2	M	20	1200	90/70-160/90
3	M	23	2400	90/60-170/100
4*	M	22	1800	90/60-200/160
5	M	20	600	90/70-170/120
6	M	19	800	90/60-180/120
7	M	35	1000	90/60-160/90
8	F	32	600	90/60-180/110

*These patients developed hypertensive crises.

During the hypertensive phase in those in whom the hypertension developed gradually the skin was pale, cold, and clammy and the patients exhibited pronounced tension and outbursts of psychomotor unrest. In all cases the hypertension responded immediately to a single dose of phentolamine 15-30 mg intravenously, phenoxybenzamine 10-20 mg daily for three or four days reducing the blood pressure to the previous low levels. With the reduction in blood pressure the other symptoms subsided. During the phenoxybenzamine treatment propranolol was continued.

In some cases the skin signs and symptoms of pronounced tension and psychomotor unrest were noted as the blood pressure began to rise. In a few further cases in which these symptoms appeared phentolamine and phenoxybenzamine given together prevented the rise in blood pressure despite continuing with the propranolol.

Discussion

Though propranolol is an antihypertensive agent, hypertensive crises may occur during its use in patients with phaeochromocytoma.³ They are thought to be caused by an unopposed alpha-receptor-constrictor response to excessive catecholamine levels. Propranolol inhibits catecholamine release, and, interestingly, most episodes of hypertension in our series occurred when the propranolol dosage was increased after a previous reduction. Presumably the reduction caused an excessive release of catecholamines, which, when the dosage was increased, acted on unopposed alpha-adrenergic receptors. These phenomena, however, may have other explanations.

Until recently the paradoxical hypertensive response to beta-blockers could be regarded as specific for phaeochromocytoma or psychosis. Then, however, a patient on methyl dopa was reported to have become hypertensive when injected intravenously with propranolol,⁴ and in another report⁵ a hypertensive woman with insulin-dependent diabetes developed a hypertensive crisis after beginning treatment with propranolol. Thus the response may occur in any patient given beta-adrenergic-blocking agents when excessive amounts of catecholamines are released.

In view of the severity of the hypertension and the effectiveness of alpha-adrenergic-blocking agents treatment should be given immediately.

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Monitoring muscle weakness in neonatal myasthenia gravis

Neonatal myasthenia gravis is rare.¹ We report a case and describe a simple method used to monitor the muscle weakness.

Patient, method, and results

The infant, a boy, was delivered by lower uterine segment caesarean section of a 26-year-old primigravida who had been diagnosed a year before as suffering from myasthenia gravis. This had progressed rapidly and was therefore classed as type 3 by the Osserman and Jenkins classification.² The infant's gestational age was 36 weeks; he weighed 2540 g and had an Apgar score of 9 at 1 minute and 9 at 5 minutes. His mouth was continuously open; there were few facial movements, and there was evident hypotonia. A poor feeder, he was described as being eager to suck but tired quickly. A positive edrophonium test confirmed the diagnosis of neonatal myasthenia gravis. He was treated with intramuscular neostigmine methylsulphate.

With a balloon (Dunlop Ltd) attached to a feeding tube which linked it to a micromanometer (250 mm WG, Furness Controls Ltd) which was in turn connected to a pen recorder (M8 Recorder Devices Ltd), the infant's sucking pressure was measured before a feed on several occasions. At 6 and 14 days of age the pressures were measured before and after an intravenous injection of 1 mg of edrophonium chloride. Before starting the study the volume of the balloon which would accurately reflect any change in pressure was determined by experiment.³ Normal, healthy, full-term infants acted as controls.

The sucking pressures were recorded when the infant was 6 days old (see fig). A dramatic improvement after intravenous edrophonium chloride was evident. The mean ($\pm$ SD) pre-feed sucking pressure for 20 full-term infants was 35 ± 6 cm H₂O. The infant's sucking pressure was monitored and a return to normal was used as a guide to stopping the neostigmine treatment. By the 14th day the sucking pressures before and after intravenous edrophonium chloride were the same. This finding correlated well with an electromyographic recording of the response to repetitive nerve stimulation, which also confirmed the absence of muscle weakness at that time. Drug treatment was therefore stopped without ill effect.

Sucking pressures recorded at 6 days in baby with neonatal myasthenia gravis.

Comment

All that was required to monitor the response to treatment of this infant with neonatal myasthenia gravis was a balloon, a pressure transducer, and a pen recorder—items of equipment available in many neonatal units.

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Unusual complication of high-dose frusemide

High-dose frusemide (1000-2000 mg/day) has been advocated in the treatment of haemodialysis patients to increase urinary output and thus permit a larger fluid intake and a more comfortable life.¹ This therapy significantly increased diuresis in about half the patients in our unit. There are few complications provided frusemide is given orally.¹⁻³ We report here an unusual side effect observed in one of our patients.

Case Report

A 49-year-old man developed rapidly progressive glomerulonephritis, proved by renal biopsy, and was started on chronic haemodialysis on 22 February 1974. Frusemide 1000 mg/day increased urine output from 300 ml to 1000 ml, and was therefore continued. White cell counts (W.B.C.) made monthly ranged between 4.47 and $6.6 \times 10^9/l$ with a normal differential count. On 19 June the patient received a cadaver kidney transplant. He retained his own kidneys. A transient episode of leucopenia and thrombocytopenia resulted from the high dose of immunosuppressive agents given. After a few weeks renal function deteriorated, oedema appeared, and 100-300 mg frusemide was given intravenously daily. On 2 August haemodialysis was resumed. Immunosuppressive therapy was interrupted four days later. The graft remained in situ. The patient was discharged on 13 August with a white cell count of $5.04 \times 10^9/l$. Frusemide, 1000 mg/day, was given orally. The only other medication was aluminium hydroxide gel 17 g/day. On 29 August the patient developed fever of 39.5°C . A leucopenia of $0.9 \times 10^9/l$ with a differential count of 72% segmented neutrophils, 6% non segmented neutrophils, 2% basophils, 4% eosinophils, 8% monocytes, and 8% lymphocytes was noted. The platelet count was normal. The findings on clinical examination were within normal limits; the results of biochemical tests were unchanged. Serological tests were normal; bacteriological cultures of blood, sputum and urine were sterile.

The hypothesis of a drug-induced leucopenia was confirmed by a lymphocyte stimulation test which provided the following results: spontaneous incorporation 70 c.p.m., frusemide 145 c.p.m. In the same test performed on 30 July the results were: spontaneous incorporation 309 c.p.m., frusemide 226 c.p.m. Frusemide was stopped on 30 August and white cell counts returned to normal within 10 days. Throughout this period platelets and packed cell volume remained stable. The therapeutic regimen, W.B.C., and platelets counts are shown in the fig.

Therapeutic regimen in relation to white cell and platelet counts.

Discussion

The commonest cause of leucopenia in a dialysis patient is the profound neutropenia induced at the start of haemodialysis by temporary sequestration of the neutrophils in the lungs.⁴ In our patient all W.B.C. counts were made before connexion to the dialyser and differential counts remained normal. That the leucopenia was related to the immunosuppressive agents given four weeks earlier is improbable: there was no leucopenia one week after interrupting azathioprine and lymphocytic antiserum, differential counts, and platelets remained normal throughout this period. In fact, the results of the lymphocyte stimulation tests and the spontaneous recovery within a few days of stopping frusemide seem to implicate this drug as the cause of the leucopenia.

The side effects usually reported with high doses of frusemide in chronic renal failure are deafness, tinnitus, hyperuricaemia, hyperglycaemia, and nausea.¹⁻³ Though the chemical structures of sulphonamides and frusemide are very similar we know of no reports of cases of granulocytopenia from using frusemide in haemodialysis patients. Rastogi *et al.*⁵ state that out of 250 white cell counts in their patients with chronic renal failure receiving frusemide up to 2000 mg/day only six gave results below $3 \times 10^9/l$, and none of these findings was substantiated on repetition without interruption of the drug. Nevertheless, frusemide may have the same leucopenic action as sulphonamides and white cell counts should be made repeatedly in every patient receiving the drug.

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