were uncontrolled. We report on a prospective randomised double-blind trial of cyclophosphamide in ACH, during which serum gonadotrophin concentrations were monitored to assess the degree of gonadal damage.

Patients, methods, and results

Ten patients with histologically proved aggressive hepatitis, a history of liver disease for more than three months, and an aspartate aminotransferase (AST; GOT) concentration greater than 150 IU/l (normal <50 IU/l) entered the trial. None had carried hepatitis virus B, and eight had positive titres of antinuclear factor or smooth muscle antibody, or both. The disease activity was first brought under "control" (AST concentration <100 IU/l) for four weeks with prednisolone, which was then reduced every two weeks by 2 mg/day until "relapse" (AST concentration >150 IU/l). The prednisolone dose was then increased fortnightly by 4 mg/day until control had been regained for four weeks. The patients were then randomly allocated to receive either cyclophosphamide 3 mg/kg in a single morning dose or placebo for 12 weeks, and the prednisolone dose was reduced. After relapse the prednisolone dose was increased, and after four weeks' control the patients were crossed over. Patients were seen fortnightly, when blood counts and gonadotrophin concentrations were estimated and liver function tests carried out. In the single male patient testosterone concentrations and sperm counts were also measured.

Responses of patients who completed trial to addition of cyclophosphamide or placebo to corticosteroid treatment

Case No	Treatment	Prednisolone dose at relapse (mg/day)	No of weeks no prednisolone before relapse	Peak AST during relapse (IU/l)	No of weeks to control
1	Cyclophosphamide	0	14	230	5
	Placebo	0	2	240	2
1	Cyclophosphamide	0	2	650	4
	Placebo	0	10	180	4
2	Cyclophosphamide	8	0	1225	24
	Placebo	0	2	875	4
3	Cyclophosphamide	2	0	1600	5
	Placebo	0	36	R	R
4	Cyclophosphamide	0	0	225	2
	Placebo	0	0	650	4
5	Cyclophosphamide	0	2	575	10
	Placebo	0	5	550	2
6	Cyclophosphamide	12	0	190	8
	Placebo	0	15	500	14

R = Remains in remission.

Four of the 10 patients did not relapse more than once after prednisolone was withdrawn and therefore did not receive both cyclophosphamide and placebo. Five patients crossed over once and one twice, providing seven pairs of data for comparison. In four pairs placebo preceded and in three followed cyclophosphamide. The table shows the outcome. In four patients the control period was longer after cyclophosphamide treatment, two patients remaining in remission without treatment for over three months, but in two a longer control period followed placebo, and in one there was no difference. There was no significant difference in the severity of the relapse or the establishment of control after the two treatment periods (Wilcoxon rank sign test: $P > 0.1$).

Complications—All six patients noticed some hair loss, which was not severe. One developed sterile haemorrhagic cystitis and two mild frequency or dysuria; these resolved on stopping treatment. Three developed leucopenia ($<2.5 \times 10^9/l$ ($2500/mm^3$)) without clinical consequences. The only male patient receiving cyclophosphamide developed testicular failure. Before treatment the sperm count was low ($13.7 \times 10^6/ml$, volume 1.4 ml, 75% motile) but plasma concentrations of follicle-stimulating and luteinising hormones were normal. After cyclophosphamide treatment he had complete azoospermia and a persistently raised plasma gonadotrophin concentration, and there was no evidence of gonadal recovery 12 months after stopping treatment. There was no consistent change in gonadotrophin concentrations in the women.

Comment

Although the prognosis is poor without corticosteroids, the course of ACH is variable; thus steroids were withdrawn without relapse in four of the 10 patients. This underlines the importance of an adequate control or placebo period in the trials of treatment and may explain previous reports of apparent success with cyclophosphamide. The number of patients in this trial was small, and a difference between the treatment and placebo periods might emerge with larger numbers. In view of the complications, however, particularly the profound and persistent azoospermia that commonly results from cyclophosphamide

treatment,⁵ the benefits would have to be striking to justify its use.

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Labetalol in severe tetanus

Curarisation can control the neuromuscular manifestations of severe tetanus, but the problem of periodic cardiovascular stimulation remains. This is an uncommon phenomenon, which may be due to interference with the hypothalamic control of vasomotor activity,¹ and may be accompanied by a rise in circulating catecholamine concentrations.^{2,3} Many drugs have been used to control this condition, with variable results. Some of the adrenergic-blocking agents can be given only by mouth, which has caused problems in administration, since gastrointestinal absorption is often impaired. Tachyphylaxis develops to others, and some have a transient effect when given intravenously. Long-term toxicity limits the use of vasodilators such as nitroprusside. Furthermore, each patient's condition varies, with predominance of tachycardia or hypertension, or both. The combined alpha- and beta-adrenergic blocking effect of labetalol⁴ and its relative lack of tachyphylaxis may be advantageous. We have shown its efficacy when given by intermittent injection, and now report on its successful administration by continuous infusion over 19 days.

Case report

A 33-year-old man cut his knee playing football. The wound was dressed at the local hospital where he was given a "booster" dose of tetanus toxoid. (There was subsequently some doubt whether he ever had toxoid before.) One week later he developed stiffness of his jaws, and on the eighth day was admitted to the respiratory and intensive care unit of the Royal Victoria Hospital. By then the clinical picture was typical of tetanus, with back pain, stiffness of jaw, tongue-biting, and some difficulty in swallowing. Sedation with diazepam and chlorpromazine eased the symptoms. He was given human tetanus antitoxin, tetanus toxoid, and antibiotics and the wound was thoroughly excised.

Tetanus progressed rapidly, and two days later he had to be curarised to control symptoms. The blood pressure and heart rate were labile and tachycardia and hypertension (systolic >200 mm Hg) were not controlled by heavy sedation. In view of the short history, it seemed likely that control of blood pressure and heart rate would be difficult. An infusion of 1 mg/min labetalol was started and pancuronium was replaced by tubocurarine. He was sedated with buprenorphine and lorazepam given alternately every three hours. This stabilised the cardiovascular symptoms for six days, when the dosage of labetalol had to be increased to 2 mg/min. Tubocurarine was stopped after eight days and again after 12 days of curarisation when it was obvious that he still had persisting signs of tetanus.

On the 19th day of curarisation labetalol and tubocurarine were again withdrawn. After eight hours curarisation was "reversed" with 5 mg neostigmine, preceded by and also mixed with 1.8 mg atropine. Despite this dose of atropine, the heart rate dropped dramatically after the neostigmine and a brief period of asystole occurred. Symptoms of tetanus were minimal, but

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, decuratisation should be performed cautiously and adequate doses of atropine must be given. This regimen merits further study.

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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.

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Antiplasmin concentrations after surgery: failure of α_2 -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.