movement. Improvements in rotational movement were seen only with the intra-articular injection.

These results might be improved if patients with pain confined to the posterosuperior region of the shoulder, which is said to respond selectively to a nerve block,⁵ were treated.

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Cholestasis induced by oestrogen after liver transplantation

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transplantation her menstrual periods resumed and were normal for four months. Severe menorrhagia then developed, resulting in anaemia. This heavy menstrual bleeding was not relieved by treatment with a low dose oral contraceptive (ethinyloestradiol 35 µg) but responded to a higher dose (50 µg). While receiving this higher dose she developed pruritus and biochemical evidence of intrahepatic cholestasis (figure). Withdrawing the oestrogen promptly relieved her pruritus and normalised the liver enzyme activities, but the menorrhagia returned. A final vaginal haemorrhage was managed with ethinyloestradiol 50 µg daily for one week. This second challenge again precipitated pruritus and hepatic dysfunction (figure).

The menorrhagia was controlled by an analogue of gonadorelin, leuporelin acetate, 1 mg daily, and she was also given transdermal oestrogen (a 50 µg patch twice weekly). A normal menstrual cycle was mimicked by giving medroxyprogesterone acetate 10 mg on days 20-27 of each cycle. This regimen produced regular withdrawal bleeding and stable haemoglobin concentrations and results of liver function tests, and she did not have pruritus.

The patient's family history was non-contributory. The donor of the liver had died from a subarachnoid haemorrhage; she had not had a history of liver disease during any of her pregnancies or when taking oral contraceptives.

Comment

The resolution of this patient's pruritus and normalisation of biochemical abnormalities after withdrawal of the high doses of oestrogen on two occasions support an aetiological association between the ethinyloestradiol and cholestasis. Further oestrogen treatment was given transdermally to avoid the first pass effect on the liver. She had not received oestrogen before liver transplantation because of the chronic hepatitis. Her age and response to the operation made fertility seem

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Successful liver transplantation is not usually associated with hepatic dysfunction, though both low grade rejection and cyclosporin can induce cholestasis.¹ Natural and synthetic oestrogens also alter hepatic excretory function, occasionally inducing overt cholestasis in susceptible women.² We report on a woman who developed cholestasis associated with oral oestrogen treatment after receiving an orthotopic liver transplant.

Case report

A 20 year old nulligravid woman had had well documented chronic active hepatitis since the age of 5, which had been confirmed by liver biopsy. Other causes of chronic hepatitis had been excluded. Despite corticosteroid treatment for 12 years cirrhosis and oesophageal varices had developed, causing recurrent severe upper gastrointestinal bleeding. Sclerotherapy had proved unsuccessful. She underwent successful liver transplantation. Postoperatively immunosuppression was maintained with cyclosporin 200 mg twice daily and prednisone 10 mg daily. Trough serum cyclosporin concentrations determined by radioimmunoassay remained in the therapeutic range (figure). Within four weeks of the operation results of liver function tests were normal.

Menarche at age 12 had been followed by normal menses, but she had become amenorrhoeic when ill with the repeated gastrointestinal haemorrhages. After

Biochemical concentrations before and after liver transplantation and during administration of ethinyloestradiol (shown by vertical stippled columns). Hatched horizontal areas indicate normal ranges

likely as pregnancy can occur after liver transplantation.³ We therefore did not perform a hysterectomy for the menorrhagia.

The patient's negative family history and the donor's negative history negate a genetic basis for cholestasis associated with pregnancy or sex hormones. Rejection of a transplant and cyclosporin, however, can induce low grade cholestasis. Oestrogen may have elicited such an underlying defect much as it can unmask primary biliary cirrhosis that first presents as cholestasis (pruritus) during pregnancy.⁴ Thus after liver trans-

plantation perhaps primed by treatment with cyclosporin oestrogen may elicit cholestasis.

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Bronchodilator effect of atrial natriuretic peptide in asthma

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Atrial natriuretic peptide relaxes vascular smooth muscle directly, but little interest has been expressed in its effect on airway smooth muscle despite an in vitro study showing a dose dependent relaxant effect on guinea pig trachea.¹ This effect has since been observed on tone induced by agonists in vitro,² and a recent in vivo study showed that infusions of atrial natriuretic peptide increased basal airway conductance and reversed bronchoconstriction induced by leukotriene D₄ in the same animal model.³ We examined the effect of infused atrial natriuretic peptide on bronchomotor tone in asthmatic subjects.

Subjects, methods, and results

We studied eight subjects (two women; mean (SD) age 39.7 (8.8) years). Each had moderately severe asthma: mean forced expiratory volume in one second was 47.2 (9.8)% of the predicted value and was improved in each subject by >25% by inhaled salbutamol. Inhaled bronchodilator agents were withheld for 10 hours, but other inhaled treatment was continued as usual. Written informed consent was obtained and the study approved by Glasgow West ethical committee.

On each of two study days an indwelling venous cannula was inserted into each forearm and the subject relaxed for 20 minutes. We then measured forced expiratory volume in one second (taken as the best of three attempts) with a dry wedge spirometer (Vitalograph) and blood pressure and pulse rate with a semiautomatic sphygmomanometer; we withdrew 20 ml blood to estimate plasma atrial natriuretic peptide concentration by radioimmunoassay⁴ and catecholamine concentrations. After these baseline measurements an intravenous infusion of either atrial natriuretic peptide or placebo was administered in a double blind, randomised manner. Doses of peptide corresponded to 0.5, 2.0, and 10.0 pmol/kg/min and were given for 20 minutes each in incremental fashion. At the end of each infusion period forced expiratory volume in one second, pulse, blood pressure, and atrial natriuretic peptide and catecholamine concentrations were measured. After the last dose had been completed the infusion was stopped and each subject received 5 mg nebulised salbutamol; final measurements were taken 20 minutes thereafter. The significance of the data was assessed by two way analysis of variance.

The forced expiratory volume in one second rose significantly at the highest rate of infusion with a mean increase of 0.50 (95% confidence interval 0.23 to 0.78) litre (equivalent to 31.5 (14.9 to 48.1)% from the baseline value ($p < 0.01$; figure). It tended to rise at an

Mean change in forced expiratory volume in one second with varying rates of intravenous infusion of atrial natriuretic peptide compared with placebo ($n=8$). Nebulised salbutamol (5 mg) was given after final infusion. Vertical bars represent 95% confidence intervals

infusion rate of 2 pmol/kg/min, but this was not significant. Overall, the response varied considerably: some subjects responded appreciably to the middle infusion dose while one subject did not respond at all even to the highest dose. No side effects were reported during the active and placebo studies. The mean plasma atrial natriuretic peptide concentration was 10 (95% confidence interval 6 to 15) nmol/l basally (normal 2-17 nmol/l); this rose to 12 (8 to 16) nmol/l, 43 (33 to 53) nmol/l, and 252 (220 to 285) nmol/l with increasing rates of infusion and had fallen to 12 (11 to 18) nmol/l 20 minutes after salbutamol.

Baseline pulse, blood pressure, and catecholamine concentrations were comparable, and variation in these measurements between the two study days was not significant.

Comment

We believe this to be the first report of the effects of atrial natriuretic peptide in asthmatic subjects; we found that it had considerable bronchodilator properties. In many tissues atrial natriuretic peptide alters intracellular events through generating cyclic guanosine monophosphate, and preliminary evidence suggests that a similar action occurs in tracheal smooth muscle.⁵ Although specific receptors have been identified in pulmonary tissue, they have not so far been found in airway smooth muscle. In lung disease atrial natriuretic peptide has been assumed to act as a pulmonary vasodilator in addition to having peripheral renal and vascular action. Our findings suggest that important effects on airway tone may also occur; further studies to explore the peptide's role in pulmonary physiology and disorders of airway tone are indicated.

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