good anti-herpes zoster virus antibody response she was thought to be immunocompetent. She was treated with intravenous acyclovir 10 mg/kg every eight hours for 10 days and improved rapidly. The pain from her skin lesions was greatly relieved, and after 48 hours of treatment she no longer had delusions or hallucinations and her ataxia was improving. After one week the skin lesions and ataxia had resolved, but partial abducent, facial, and vestibulocochlear palsies persisted.

Comment

Herpes zoster associated encephalitis was diagnosed in this patient from clinical features and the typical cerebrospinal fluid and electroencephalographic findings. Six months later she remained well, with no evidence of immunosuppression. Her abducent and facial nerve palsies resolved but the deafness in her left ear remained. Serum zoster titres decreased to 1/8.

Intravenous acyclovir has been effective in the treatment of severe cutaneous zoster in immunocompetent[1] and immunocompromised[2] adults. It has also proved effective in treating herpes simplex encephalitis.[3] There has not to our knowledge been a study of the use of acyclovir in herpes zoster associated encephalitis. Six patients with disseminated malignancy or other profound immunosuppression all improved dramatically within 24 hours of starting treatment with acyclovir.[4,5]

Our patient had no evidence of immunosuppression at diagnosis or afterwards and the dramatic clinical improvement was temporally related to the start of treatment with acyclovir.

1 Bean B, Braun C, Balfour HH. Acyclovir therapy for acute herpes zoster. *Lancet* 1982;ii:118-22.
2 Balfour HH, Bean B, Laskin OL, *et al.* Acyclovir halts progression of herpes zoster in immunocompromised patients. *N Engl J Med* 1983;**308**:1448-52.
3 Skoldenberg B, Alestig K, Burman L, *et al.* Acyclovir versus vidarabine in herpes simplex encephalitis. *Lancet* 1984;ii:707-11.
4 Steele RW, Keeney RE, Bradsher RW, *et al.* Treatment of varicella zoster virus meningoencephalitis with acyclovir and demonstration of virus in CSF. *Am J Clin Pathol* 1983;**80**:57-60.
5 Cheesbrough JS, Finch RG, Ward MJ. A case of herpes zoster associated encephalitis with rapid response to acyclovir. *Postgrad Med J* 1985;**61**:145-6.

(Accepted 22 September 1986)

Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 0HS
MOIRA K B WHYTE, BSC, MB, senior house officer
P W IND, MA, MRCP, consultant physician

Correspondence to: Dr Whyte.

Resolution of diabetic cheiroarthropathy

We report on two patients with diabetic sclerosis or cheiroarthropathy in whom both skin and joint changes resolved completely. In one case this improvement seemed to be related to better diabetic control. This is the first time such improvement has been reported.

Case reports

The flexion contractures of the interphalangeal joints of the hands were assessed in the two patients by the method of Grgic *et al*,[1] which we use routinely in evaluating such diabetic patients. The patient's hands are placed palm down on a table top with fingers spread. These fingers are then viewed by the examiner at table level and the contact of the fingers with the table determined. Normally the entire palmar surface of the fingers makes contact. Patients are classified as having stage 1 disease if they are unable to make contact with some portion of one finger and stage 2 disease if unable to make contact with two or more fingers.

Skin thickness was assessed over the fingers as outlined by Siebold[2]: 0=R normal; 1+ = slight but definite thickening with inability to tent the skin between the examiner's thumbs; 2+ = mild to moderate changes; 3+ = severe thickening; 4+ = extreme thickening.

Glycosylated haemoglobin concentration was estimated using electrophoresis on cellulosic matrix (Glyco-Phore, Gelman Sciences Ltd) (normal range up to 8·5%).

Case 1—A 16 year old girl with an 11 year history of insulin dependent diabetes mellitus developed limited movement of all interphalangeal joints in her hands with associated tightening and thickening of overlying skin. She was classified as having stage 2 disease and skin thickness 2+. The symptoms developed after three months of poor diabetic control when she had a persistently raised blood glucose concentration and a haemoglobin A_1 concentration of 11%. With improved diabetic control the hand changes resolved completely over five weeks. She did not have any evidence of microvascular diabetic complications.

Case 2—A 58 year old man (interestingly, the father of the patient in case 1) with a 12 year history of insulin dependent diabetes mellitus developed a clinical picture similar to that of his daughter. He was classified as having stage 2 disease and skin thickness 2+. The symptoms occurred after five months of erratic diabetic control, although the haemoglobin A_1 concentration was only 9·7%. With improved diabetic control the hand changes resolved completely over five months. He did not have any microvascular complications.

Comment

Flexion contractures of interphalangeal joints are well described in insulin dependent diabetics, various series suggesting an incidence of 20-30%.[1-3] In some these contractures are associated with skin that is waxy or has a sclerodermatous appearance, and the terms diabetic sclerosis and diabetic cheiroarthropathy have been used to describe this.

Interest in the pathogenesis of this condition is heightened by suggestions that those who develop joint contractures are at an increased risk of developing microvascular diabetic complications.[3] Joint contractures, and more recently skin thickness, in these patients have been correlated with the duration of diabetes. Workers have suggested that these clinical changes reflect abnormal non-enzymatic glycosylation of collagen, and it has been shown experimentally in rats that these changes in liver, kidney, and haemoglobin are reversible. Such reversibility was not shown to occur in collagen.[4] This contrasts with the findings in our patients, in whom apparently typical skin and joint changes resolved completely. Resolution of joint contractures has not previously been described, although in a small study skin thickness measured by ultrasonography decreased with improved diabetic control.[5]

Any theory that is advanced to explain diabetic cheiroarthropathy must take account of the potential reversibility of these changes. Observations need to be performed on several occasions in affected patients to evaluate the clinical course more fully.

1 Grgic A, Rosenbloom AL, Webber FT, Giordano B, Malone GI, Shuster JJ. Joint contracture—common manifestations of childhood diabetes mellitus. *J Pediatr* 1976;**88**:584-8.
2 Siebold JR. Digital sclerosis in children with insulin dependent diabetes mellitus. *Arthritis Rheum* 1982;**25**:1357-61.
3 Rosenbloom AL, Silverstein JH, Lezotte DC, Richardson K, McCallum M. Limited joint mobility in childhood diabetes mellitus indicates increased risk of microvascular disease. *N Engl J Med* 1981;**305**:191-4.
4 McLennan S, Yue DY, Marsh M, *et al.* The prevention and reversibility of tissue non-enzymatic glycosylation in diabetes. *Diabetic Medicine* 1986;**3**:141-6.
5 Lieberman LS, Rosenbloom AL, Riley WJ, Silverstein JH. Reduced skin thickness with pump administration of insulin. *N Engl J Med* 1980;**303**:940-1.

(Accepted 18 September 1986)

Departments of Dermatology and Medicine, Leicester Royal Infimary, Leicester LE1 5WW
DOROTHY M LISTER, MRCP, dermatology registrar
ROBIN A C GRAHAM-BROWN, BSC, MRCP, consultant dermatologist
ANDREW C BURDEN, MD, MRCP, consultant physician

Correspondence to: Dr Graham-Brown.

Alveolitis and haemolytic anaemia induced by azapropazone

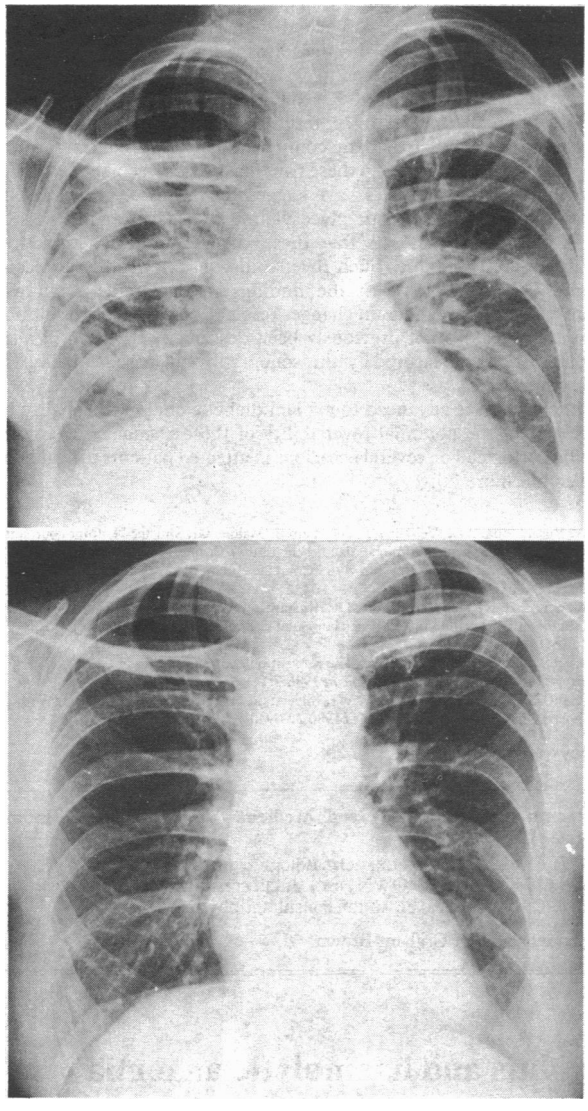
Increasing numbers of drugs have been identified as causing pulmonary disease.[1] Non-steroidal anti-inflammatory drugs may seriously depress haemopoiesis, and immune haemolytic anaemia has also been reported.[2,3] We report three cases of both reversible pulmonary infiltration and haemolytic anaemia in patients who had been taking azapropazone for nine to 18 months.

Case reports

Case 1—A 60 year old woman with an 18 month history of rheumatoid arthritis was treated initially with azapropazone and indomethacin, but both drugs were stopped when a rash developed. After a short course of prednisolone azapropazone was restarted. Eight months later she was admitted to hospital with haemolytic anaemia, breathlessness, and widespread pulmonary crackles. Haemoglobin concentration was 98 g/l and reticulocyte count 22%. A direct Coombs test yielded a positive result. A chest *x* ray film showed bilateral pulmonary infiltrates. Azapropazone was stopped, and she recovered fully after treatment with corticosteroids. Fifteen months later azapropazone was restarted, but after three weeks she again became breathless with fresh pulmonary infiltration. She responded well to corticosteroid treatment after azapropazone was stopped, and one month later there were no abnormal clinical or radiological signs.

Case 2—A 70 year old woman presented with a three week history of breathlessness. She had received azapropazone 600 mg twice daily for nine months because of a painful osteoarthritic knee. She was breathless at rest, with

crackles throughout both lungs. Haemoglobin concentration was 83 g/l and reticulocyte count 64%. A direct Coombs test gave a positive result. A chest x ray film showed infiltration throughout both lung fields. Spirometry elicited a restrictive ventilatory defect. Transbronchial lung biopsy showed severe atypical alveolar cell hyperplasia. After treatment with prednisolone and cyclophosphamide and withdrawal of azapropazone she recovered rapidly. Six months later clinical and radiological features and her blood count were normal; the result of a Coombs test was negative.



Radiographs obtained at presentation (top) in case 3 and four weeks later (bottom).

Case 3—A 53 year old woman presented with a four month history of breathlessness. She had a 20 year history of psoriatic arthropathy and had been prescribed various analgesic and anti-inflammatory drugs. Eighteen months before admission she had started taking azapropazone 600 mg twice daily. She was breathless at rest with normal breath sounds. Haemoglobin concentration was 101 g/l. A direct Coombs test yielded a strongly positive result. The antinuclear antibody titre was greater than 1/320 (homogenous IgG), and a latex test gave a negative result. A chest x ray film (figure) showed bilateral pulmonary infiltration (a routine film taken three years earlier had been normal). Pulmonary function tests showed a restrictive ventilatory defect with reduced lung volumes. Because of the earlier cases we suspected a drug induced reaction; azapropazone was therefore stopped and treatment with prednisolone started. Her symptoms resolved within two weeks. Despite the withdrawal of prednisolone she remained symptom free for 18 months. Chest radiographic appearances, results of lung function tests, and blood count returned to normal within four weeks.

Comment

Pulmonary infiltration has been described in patients treated with non-steroidal anti-inflammatory drugs; phenylbutazone, sulindac, and naproxen have been implicated.[4 5] Our patients had pulmonary infiltration with haemolytic anaemia suggestive of an allergic or immune reaction. Results of lung function tests in two cases were consistent with alveolitis. The rapid resolution of the clinical, radiological and physiological features when azapropazone was withdrawn and prednisolone given strongly suggests a drug induced reaction, as does the recurrence of symptoms on rechallenge (case 1).

Since 1976 the Committee on Safety of Medicines has received 11 reports of allergic alveolitis, pulmonary fibrosis, or fibrosing alveolitis and 18 reports of haemolytic anaemia in patients taking azapropazone. There has been only one previous report suggesting that a combination of alveolitis and haemolytic anaemia was associated with azapropazone. Here we report three additional cases. In response to these cases both haemolytic anaemia and alveolitis have been added to the adverse reaction section of the data sheet for azapropazone (Rheumox).

We acknowledge the help of Dr J F Hort, director of medical services, A H Robins Co Ltd; and Miss Claire Wiltshire, Mrs Elsie Miller, and Miss Margaret Bayliff for typing the manuscript.

1 Rosenow EC. The spectrum of drug-induced pulmonary disease. *Ann Intern Med* 1972;77:977-91.
2 Scott GL, Myles AB, Bacon PA. Autoimmune haemolytic anaemia and mefenamic acid therapy. *Br Med J* 1968;iii:534-5.
3 Korsager S. Haemolysis complicating ibuprofen treatment. *Br Med J* 1978;i:79.
4 Thurston JG, Marks P, Trapnell D. Lung changes associated with phenylbutazone treatment. *Br Med J* 1976;ii:1422-3.
5 Buscaglia AJ, Cowden FE, Brill H. Pulmonary infiltrates associated with naproxen. *JAMA* 1984;251:65-6.

(Accepted 25 September 1986)

Ham Green Hospital, Bristol BS20 0HW
M K ALBAZZAZ, MB, MRCP, medical registrar
J E HARVEY, MD, MRCP, consultant physician
J N HOFFMAN, MB, BS, consultant physician

Royal Devon and Exeter Hospital, Exeter EX2 5DW
J A SIDDORN, MB, MRCP, consultant physician

Correspondence to: Dr Harvey.

Bronchoconstriction induced by nebulised ipratropium bromide: relation to the bromide ion

Ipratropium bromide is a synthetic anticholinergic bronchodilator that is now widely used to treat acute and chronic airflow obstruction. In recent years at least 30 cases have been reported in which bronchoconstriction rather than bronchodilatation occurred after its administration as a nebulised solution. Connolly suggested that the bronchoconstriction might be secondary to an increase in sputum viscosity,[1] and Jolobe postulated an idiosyncratic response of bronchial smooth muscle to anticholinergic drugs.[2] We proposed that the most likely explanation was hypotonicity of the original nebulised solution marketed.[3] Thus the original nebuliser solution and its vehicle, both in hypotonic form, produced bronchoconstriction in asthmatic patients who had greatly increased non-specific airways reactivity, whereas this response was not observed when the solutions were rendered isotonic.[4] As a result of these studies Boehringer Ingelheim reformulated ipratropium bromide nebuliser solution to be isotonic. Nevertheless, Patel and Tullett described a case of bronchoconstriction in response to isotonic ipratropium bromide nebuliser solution and suggested that the bronchoconstriction was probably due to an adverse reaction to the inhaled bromide ions.[5] We report the effect of inhaled bromide ions on airway calibre in asthmatic patients who had developed bronchoconstriction on inhaling the original, hypotonic ipratropium bromide nebuliser solution.

Patients, methods, and results

We studied nine asthmatic patients. All had considerable non-specific airways hyper-reactivity to methacholine (geometric mean provocation concentration required to produce a 20% fall in the forced expiratory volume in one second=0·39 (range 0·13-0·64) mg/ml) and had previously developed bronchoconstriction after inhaling hypotonic ipratropium bromide nebuliser solution. The patients attended the laboratory on four separate days after omitting their usual medication for at least six hours. On each study day they received one of four nebulised solutions: isotonic ipratropium bromide (296 mmol/kg; 127 g/kg), isotonic sodium chloride, isotonic sodium bromide, and hypotonic sodium bromide (7·5 mmol/kg; 1·4 g/kg). All solutions were nebulised with an Inspiron minijet nebuliser at a flow rate of 8 l/min from a starting volume of 4 ml. Patients inhaled the aerosols through a mouthpiece