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.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 The rapid resolution of the clinical, radiological and physiological features when azapropazone was withdrawn and prednisolone given strongly suggests a drug induced reaction, as does the recurrence of symptoms on rechallenge (case 1).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).

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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

Mean (SEM) changes in forced expiratory volume in one second, expressed as percentage of baseline value, after inhalation of hypotonic sodium bromide solution (■), isotonic sodium bromide solution (●), isotonic sodium chloride solution (◆), and isotonic ipratropium bromide nebuliser solution (▲).

during tidal breathing for three minutes; under these conditions roughly 1 ml of solution was delivered by the nebuliser. Measurements of forced expiratory volume in one second and forced vital capacity were made before and 2, 5, 10, 15, 30, and 45 minutes after nebulisation. Responses to the various inhalations were analysed by three way analysis of variance and Duncan's multiple range test.

There were no significant differences in the baseline forced expiratory volumes in one second on any of the four study days. Inhalation of hypotonic sodium bromide produced bronchoconstriction, with the mean maximum fall in the forced expiratory volume in one second (24.0 (SEM 5.3)%) occurring two minutes after inhalation ($p < 0.01$). Inhalation of the three remaining test solutions produced no significant change in airway calibre (figure 1).

Comment

In this study bromide ions administered in the form of isotonic sodium bromide or isotonic ipratropium bromide did not produce significant bronchoconstriction in asthmatic patients who had previously developed bronchoconstriction after inhaling the original hypotonic ipratropium bromide nebuliser solution. The only solution that produced bronchoconstriction was the hypotonic sodium bromide, which had no effect on airway calibre when made isotonic. The patient reported on by Patel and Tullett developed bronchoconstriction in response to ipratropium bromide and sodium bromide dissolved in isotonic saline,⁵ and this response was probably due to an idiosyncratic reaction to bromide ions. As none of the nine patients in the present study developed such a response it seems an unlikely explanation for the bronchoconstriction observed with the previously marketed ipratropium bromide, and we conclude that the major problem was hypotonicity of the solution. The current preparation of ipratropium bromide available for nebulisation is isotonic, which therefore circumvents the original problem of bronchoconstriction induced by hypotonicity.

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Medicine 1, Centre Block, Southampton General Hospital, Southampton SO9 4XY

P RAFFERTY, MRCP, research fellow

R BEASLEY, FRACP, research fellow

PH HOWARTH, MRCP, lecturer in medicine

J S MANN, MRCP, research fellow

S T HOLGATE, MD, FRCP, professor of medicine

Correspondence to: Dr Rafferty.

Endocarditis prophylaxis: Do patients remember advice and know what to do?

The incidence and mortality of infective endocarditis remain high despite attempted prophylaxis, potent antibiotics, and advances in cardiac surgery. Organisms from the mouth and pharynx are the commonest infecting agents.¹ In a recent national survey, however, only a few patients had received recent dental treatment,^{1,2} and in some patients dental sepsis was recognised as the probable source of endocardial infection. Good, regular dental care has been emphasised as being important in endocarditis prophylaxis, in addition to other measures.^{2,3} In a survey of patients known to be at risk of endocarditis and attending hospital for regular cardiological review we examined the nature and effect of previous advice about endocarditis prophylaxis.

Patients, methods, and results

One hundred and thirty four patients attending five cardiology clinics for routine review of valvular or congenital heart disease answered a simple questionnaire. Edentulous patients were excluded. Patients were asked: (a) had they received advice about their teeth in relation to their heart condition? (b) if so, what was it? (c) how often did they visit their dentist? and (d) when did they last visit a dentist? The teeth and gums were inspected by the reviewing doctor and categorised as healthy, having mild disease, or having severe sepsis. The hospital notes were searched for any recorded advice on endocarditis prophylaxis. The date of the most recent recorded advice and the total duration of follow up were noted.

The table shows the results of the questionnaire and the dental inspection. Less than one fifth of the patients knew that it was important both to have good dental health and to receive antibiotic cover for dental procedures. Almost a third of the patients visited their dentist only when they had dental symptoms, and almost a quarter had not seen a dentist for more than a year. With one exception severe sepsis was present only in patients who did not have regular dental checks. Of 20 patients with previous endocarditis, four did not have regular dental attention, but all knew of the need for antibiotic prophylaxis.

Results of questionnaire and dental inspection

	No of patients
Recall by patient of receiving advice:	
No memory of any advice	30
Advice recorded in notes	10
No record of advice	20
Remembered receiving advice	104
On good dental health and antibiotic cover	24
On antibiotic cover only	67
On good dental health only	3
Wrong or vague information	10
Frequency of routine dental checks:	
At least every six months	87
Every six to 12 months	5
Every one to two years	0
Only when necessary	42
Date of last visit to dentist:	
Within 6 months	89
Six to 12 months ago	13
One to two years ago	12
More than two years ago	20
Result of dental inspection:	
Apparently healthy	94
Saw dentist within six months	73
Saw dentist more than six months ago	21
Mild disease	32
Saw dentist within six months	15
Saw dentist more than six months ago	17
Severe sepsis	8
Saw dentist within six months	1
Saw dentist only when necessary	7

In more than half the cases (68/134) the hospital notes contained no record of advice on prophylaxis being given. Of 30 patients who denied receiving any advice, however, 10 had notes stating that advice had been given. Prophylactic advice had been sent to the family doctor in 59 cases, and in 38 there was a record of verbal advice to the patient. In 23 patients the last recorded endocarditis prophylaxis advice was at least five years before.

Comment

Our results show that, despite previous attention to this problem,⁴ many patients known to be at risk of endocarditis are ignorant of currently recommended prophylaxis. Previous strong emphasis on the "dangers" of