Bronchospasm induced by isotretinoin

Drs R A SABROE, R C D STAUGHTON, and C B BUNKER (Department of Dermatology, Westminster and Chelsea Hospital, London SW10 9NH) write: We report a case of bronchospasm occurring during treatment with isotretinoin.

A 16 year old boy with resistant acne and a long history of atopic eczema and mild asthma (requiring only intermittent salbutamol) was treated with isotretinoin (Roaccutane). Within one month of the start of treatment his asthma had deteriorated, with symptoms of exercise induced bronchospasm and nocturnal waking. He required high dose inhaled corticosteroids (beclomethasone 500 µg twice daily) and β₂ agonists for symptom control. His respiratory symptoms resolved completely when isotretinoin was stopped and the inhaled corticosteroids were withdrawn with no worsening in asthma control. This was his first recorded significant exacerbation of asthma and there were no other clear precipitating factors. Eighteen months later the patient requested a further course of isotretinoin for his acne. Once again his asthma deteriorated, and treatment was withdrawn after two weeks.

Pulmonary side effects of isotretinoin have not been widely reported. However, a case of exercise induced bronchoconstriction was reported in an atopic patient after oral isotretinoin treatment.¹ Additionally, over the past 10 years the manufacturers of Roaccutane have received 31 reports of asthma occurring during treatment, of which 18 can be substantiated. In a controlled study patients with acne taking isotretinoin showed a significant reduction (approximately 0.5 litres) in the forced expiratory flow rate at 50% vital capacity, which causes a distortion in the shape of the flow volume loop and attests to small airway disease.² In the treatment of systemic sclerosis isotretinoin has been reported to cause an eosinophilic pleural effusion³ and to be associated with a decline in lung volumes and decreased carbon monoxide transfer.⁴ Finally, the manufacturers of isotretinoin have on record isolated reports of pleural effusion, interstitial fibrosis, re-

current pneumothorax, pulmonary granulomata, and deterioration in lung function tests occurring during, but not necessarily attributable to, treatment with isotretinoin.

Retinoids may produce a drying effect on the respiratory tract similar to that which occurs in the skin and mucous membranes, and this may in some way increase the tendency towards asthma in atopic patients.¹

- 1 Fisher DA. Exercise induced bronchoconstriction related to isotretinoin therapy. *J Am Acad Dermatol* 1985;13:524.
- 2 Bunker CB, Tomlinson MC, McI Johnson N, Dowd PM. Isotretinoin and the lung. *Br J Dermatol* 1991;125(suppl 38):29.
- 3 Bunker CB, Sheron N, Maurice PDL, Kocjan C, McI Johnson N, Dowd PM. Isotretinoin and eosinophilic pleural effusion. *Lancet* 1989;ii:435-6.
- 4 Bunker CB, Maurice PDL, Little S, McI Johnson N, Dowd PM. Isotretinoin and lung function in systemic sclerosis. *Clin Exp Dermatol* 1991;16:11-3.

Ranitidine and aseptic meningitis

Drs J M DURAND and L SUCHET (Departments of Internal Medicine and Neurology, Sainte-Marguerite Hospital, Marseilles, Cedex 9, France) write: In June 1993, two weeks after taking ranitidine, a 30 year old man was admitted with fever and meningism. His cerebrospinal fluid was abnormal, with white blood cell count of 223×10⁹/l, a polymorphonuclear leucocyte concentration of 80%, a protein concentration of 1.2 g/l, and a glucose concentration of 2.9 mmol/l. Ranitidine was stopped, and the patient was treated with cefotaxime and perfloxacinmesylate with a prompt response. In October he was readmitted 24 hours after he had received ranitidine with clinical and laboratory features as on the previous admission. The drug was stopped and within 72 hours he was free of symptoms without any treatment. Seven days later, analysis of the cerebrospinal fluid yielded normal results. In November, one hour after taking ranitidine, symptoms recurred. The drug was stopped and intravenous acyclovir was given. Within 72 hours the fever had abated, and he had fully recovered by the following day. The patient reported xerostomia, and a labial salivary gland biopsy specimen was

suggestive of Sjögren's syndrome; he had nuclear and skin sensitising antibodies.

The consistent inability to identify a bacterial, fungal, or viral pathogen, the temporal relation of the illness to ranitidine treatment, and the dramatic recovery on withdrawal of the drug suggest that this case is another example of drug induced aseptic meningitis. The patient was advised to avoid H₂ receptor antagonists and he had no recurrence of meningitis during 12 months of follow up.

The mechanism of drug induced aseptic meningitis is not known, but several cases have been reported in patients with connective tissue disease^{1,2} possibly indicating a role of the immune system in drug induced meningitis. Differentiating between infection, exacerbation of underlying disease, and the possibility of an adverse drug reaction may be exceedingly difficult, but adverse reactions must be kept in mind with ranitidine.

- 1 Joffe AM, Farley JD, Linden D, Goldsand G. Trimethoprim-sulfamethoxazole-associated aseptic meningitis: case reports and review of the literature. *Am J Med* 1989;87:332-8.
- 2 River Y, Averbuch-Heller L, Weinberger M, Meiner Z, Mevorach D, Schlesinger I, et al. Antibiotic induced meningitis. *J Neurol Neurosurg Psychiatry* 1994;57:705-8.

Pravastatin: interaction with oral anticoagulant?

Drs THIERRY TRENQUE and HENRI CHOISY, and MARIE-LAURE GERMAIN, pharmacist (Centre Régional de Pharmacovigilance, Laboratoire de Pharmacologie, Hôpital Maison Blanche, 51092 Reims, France) write: Pravastatin is a hydrophilic competitive inhibitor of 3-hydroxy-3-methyl glutaryl coenzyme A, the enzyme responsible for the rate limiting step of endogenous cholesterol synthesis. Interaction studies with oral anticoagulants have shown no change in prothrombin time or in the pharmacokinetic variables of pravastatin.¹ On the other hand, when lovastatin² or simvastatin³ and coumarin are administered concomitantly, prothrombin time may be increased in some patients. The clinical safety profiles of these agents are similar.

After atrial fibrillation, anticoagulants are used to prevent any thromboembolic complications in patients. Moreover, this disorder

can be associated with type IIb hypercholesterolaemia. If dietary weight reduction has no effect, treatment with fibric acid derivative or 3-hydroxy-3-methyl glutaryl coenzyme A (HMG CoA) reductase inhibitors can be started. However, fibrate enhances the effect of anticoagulants,⁴ and lovastatin or simvastatin given with warfarin increase prothrombin time slightly.⁵ We report a case of interaction between an oral anticoagulant and pravastatin.

A 64 year old woman with atrial fibrillation was given 20 mg flutidone (an orally administered indanedione anticoagulant) daily as prophylaxis for any thromboembolic event. Her international normalised ratio was stable between 2.5 and 3.5. Diet and appropriate exercise did not have any effect on her cholesterol (9.03 mmol/l) and triglyceride (5.27 mmol/l) concentrations. Pravastatin 10 mg was given for the control of hypercholesterolaemia; five days later haematuria appeared. Laboratory tests showed an international normalised ratio of 10.2. Treatment was stopped; the bleeding resolved completely over the next 72 hours and international normalised ratio was 3.8.

In patients with simvastatin or lovastatin added to anticoagulant therapy, monitoring of international normalised ratio must be monitored more frequently during early treatment and should perhaps be extended when patients are given pravastatin in addition to anticoagulants. Unlike other 3-hydroxy-3-methyl glutaryl coenzyme A reductase inhibitors, binding interaction does not seem to be implicated since the protein binding of pravastatin is about 50%. The hypothesis of hepatic metabolic interaction may be evoked.

- 1 McTavish D, Sorkin EM. Pravastatin: a review of its pharmacological properties and therapeutic potential in hypercholesterolemia. *Drugs* 1991;42:65-89.
- 2 Tobert JA, Shear CL, Chremos AN, Mantell GE. Clinical experience with lovastatin. *Am J Cardiol* 1990;65:23-6.
- 3 Walker JF. Simvastatin: the clinical profile. *Am J Med* 1989;87:445-65.
- 4 Reynolds JEF, ed. Clofibrate and other lipid regulating agents. In: *The extrapharmacopoeia*. 30th ed. London: Pharmaceutical Press 1993:979-94.
- 5 Wolterbeek R. Adverse effects of cholesterol synthesis inhibitors. *Ned Tijdschr Geneesk* 1993;13:973-7.

ONE HUNDRED YEARS AGO

REGISTRATION OF UNDERTAKERS.

This is the age of registration. Like love in the old French proverb, registration is, was, or will be master of all of us. Now it is the turn of the undertakers. A law has been passed in Pennsylvania creating a State Board of undertakers in the cities of the first, second, and third classes. The law requires systematic examinations, registrations, and licences for all entering the business of burying the dead. All applicants

for licences must be examined by the Board and found to be possessed of good moral character, skill and knowledge of sanitation, preservation of the dead, disinfecting the bodies of deceased persons, and the apartment, clothing, and bedding in case of death from infectious or contagious diseases. All persons receiving a licence from the State Board of undertakers must register at the office of the Board of Health at the city in which it is proposed to carry on business. (*BMJ* 1896; i:103.)