Pulmonary toxicity of malaria prophylaxis

A C Davidson, C Bateman, C Shovlin,
M Marrinan, G H Burton, I R Cameron

Departments of Medicine
and Cardiothoracic
Surgery, United Medical
and Dental Schools of
Guy's and St Thomas's
Hospitals, London
SE1 7EH

A C Davidson, MRCP, *lecturer
in medicine*
C Bateman, *medical student*
C Shovlin, MB, *house
physician*
M Marrinan, FRCS, *registrar*
I R Cameron, FRCP, *professor
of medicine*

Medicines Division,
Department of Health and
Social Security, London
G H Burton, MRCP, *senior
medical officer*

Correspondence to: Dr
Davidson.

The increased use of malaria prophylaxis has led to more reports of drug induced toxicity. Hepatic, renal, skin, and bone marrow effects are well recognised. Five cases of pulmonary toxicity and systemic illness after the use of pyrimethamine-sulfadoxine (Fansidar) have been reported.^{1,2} In two of these reports rapidly progressive respiratory failure developed and open lung biopsy showed eosinophilic pneumonia. We report four cases of pulmonary eosinophilia: three patients became ill after taking pyrimethamine-dapsone (Maloprim; Wellcome) and one after taking pyrimethamine-chloroquine (Daraclor; Wellcome).

Case reports

The table gives details of the patients and summarises the investigations and outcome. One patient had previously taken chloroquine prophylactically (case 2). We screened two patients (cases 1 and 2) for infection, which included performing sputum, blood, and lung tissue culture and serological tests for legionella, mycoplasma, chlamydia, and the respiratory viruses. To exclude other causes of pulmonary eosinophilia stools were examined for ova and parasites and serological tests for trichinella, toxocara, schistosoma, and filaria performed.

Case 1—The persistently low titre of schistosomal antibodies on enzyme linked immunosorbent assay (ELISA) probably indicated previous infection. After Maloprim was stopped multiple antibiotics were pre-

scribed and the patient improved clinically over three weeks. After her return to the United Kingdom she had a cardiorespiratory collapse and an open lung biopsy was performed. She admitted to self treatment with Maloprim two hours before the collapse. Steroids (30 mg prednisolone) led to a dramatic clinical and radiological improvement. A lymphocyte transformation test was performed three weeks later by incubating her cells with dapsone and pyrimethamine. No reaction occurred with either drug.

Case 2—Pulmonary infarction resulting from an eosinophilic vasculitis associated with a florid eosinophilic pneumonia caused the clinical deterioration of this patient. His condition initially improved when Maloprim and chloroquine were withdrawn, although steroids were later necessary.

Case 3—Pulmonary eosinophilia was suspected, and rapid improvement occurred without treatment when Maloprim was stopped.

Case 4—The patient recovered without taking antibiotics or steroids when Daraclor was withdrawn. The initial diagnosis was sarcoidosis, but the complete radiological and clinical recovery after 10 days suggested an allergic reaction.

Comment

The five cases of pulmonary toxicity previously reported were typical of pulmonary eosinophilia.^{1,2} Histological confirmation of pulmonary eosinophilia was obtained in two of the patients in this study. Although lung biopsy was not performed in cases 3 and 4, pulmonary eosinophilia was likely despite the absence of a peripheral blood eosinophilia in case 3. In the absence of any other cause (food and fungal allergy and infection with helminths were excluded as far as possible) we believe that the antimalaria drugs were responsible for the toxic reaction. The evidence was particularly strong in case 1 as rechallenge with

Results of investigations in four patients with pulmonary toxicity and systemic illness after taking antimalarial drugs containing pyrimethamine

	Case 1	Case 2	Case 3	Case 4
Sex	F	M	F	F
Age (years)	23	31	37	47
History	Mild atopic asthma	Chloroquine previously taken uneventfully		
Treatment (duration) (weeks)	Maloprim (pyrimethamine-dapsone) (4)	Maloprim (pyrimethamine-dapsone) and chloroquine (5)	Maloprim (pyrimethamine-dapsone) (3)	Daraclor (pyrimethamine-chloroquine) (3)
Symptoms	Myalgia, fever, cough, progressive breathlessness	Fever, vomiting, macular rash, severe breathlessness	Cough, malaise, fever	Fever, cough, breathlessness
Results of investigations:				
Radiology	Consolidation in upper zone initially, subsequently widespread with transient pleural effusions	Nodular progressing to patchy consolidation bilaterally	Patchy consolidation bilaterally	Widespread nodular shadowing
Haematology				
Haemoglobin (g/l)	104 (normocytic normochromic anaemia)	124	108 (normocytic normochromic anaemia)	126
Total white cell count ($\times 10^9/l$)	11.8-14.5	27.2	12.4	<0.4
Eosinophil count ($\times 10^9/l$)	0.4-0.7 initially, 3.1-4.4 subsequently	4.5	2.1	<0.4
Erythrocyte sedimentation rate (mm in first hour)	107-115	5	115	64
Arterial oxygen tension (kPa)	13.2 before challenge with Maloprim, * 5.1 after	5.9-7.3	Not done	Not done
Biochemistry	Alkaline phosphatase activity 2 $\times$ normal	Normal	Normal	Serum angiotensin converting enzyme 140 IU/l (normal <56); alkaline phosphatase activity 3 $\times$ normal; serum alanine aminotransferase activity 10 $\times$ normal
Screen for infection	Schistosomal ELISA positive (grade 3)	Negative	Negative	Negative
Biopsy	Eosinophilic pneumonia	Eosinophilic pneumonia with pulmonary infarction	Not done	Mild granulomatous hepatitis; Kveim test negative
Progress	Full recovery with steroids lymphocyte transformation test negative	Initial improvement on withdrawal of drug. Sudden deterioration with pleurisy and haemoptysis. Full recovery with steroids	Pulmonary eosinophilia suspected. Full recovery when drug withdrawn	Full recovery when drug withdrawn

ELISA = Enzyme linked immunosorbent assay.
*Challenge resulted in cardiorespiratory collapse.

Maloprim by the patient had near fatal results. Pyrimethamine was taken by all four patients, suggesting that this may have been the toxic agent.

Previous workers assumed that the sulphonamide component of Fansidar was responsible for the pulmonary toxicity.^{1,5} In one report a lymphocyte transformation test yielded positive results in the presence of sulfadoxine but also with pyrimethamine, perhaps suggesting that non-specific cell activation had occurred.³ We were unable to show lymphocyte activation with either dapsone or pyrimethamine, but this was assessed in only one patient and then only after she had recovered and taken steroids. Dapsone, the other constituent of Maloprim, is structurally related to the sulphonamides. Nevertheless, despite its widespread use it has not been reported to cause pulmonary eosinophilia. Similarly there are no reports of pulmonary toxicity with chloroquine. Three further cases of pulmonary eosinophilia, one confirmed by lung biopsy, have been reported to Wellcome Research Laboratories in patients who had taken Maloprim, and two cases of pulmonary toxicity with systemic features

have been reported in patients who had taken pyrimethamine-chloroquine (L Maskell, personal communication). We therefore believe that pyrimethamine may cause pulmonary eosinophilia.

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- 4 Murphy RL, Phair JP. Systemic reaction to pyrimethamine-sulfadoxine. *J Fam Pract* 1986;22:375-6.
- 5 McCormack D, Morgan WKC. Fansidar hypersensitivity pneumonitis. *Br J Dis Chest* 1987;81:194-6.

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Plasma methionine enkephalin concentration and prognosis in primary biliary cirrhosis

J R Thornton, M S Losowsky

Department of Medicine,
St James's University
Hospital, Leeds LS9 7TF
J R Thornton, MRCP, lecturer
M S Losowsky, FRCP,
professor

Correspondence to: Dr
Thornton.

Plasma methionine enkephalin concentration is increased in patients with cirrhosis and ascites but is often normal in patients with compensated cirrhosis without ascites.¹ It may, therefore, reflect the severity and prognosis of the cirrhosis. We measured plasma methionine enkephalin concentrations in 34 patients with primary biliary cirrhosis of various stages of severity and monitored the clinical course of the disease.

Patients, methods, and results

We diagnosed primary biliary cirrhosis on the basis of the clinical presentation and results of histological examination of the liver. Mitochondrial antibodies (>1/100) were present in 28 patients.

We collected venous blood samples and measured concentrations of methionine enkephalin by radioimmunoassay (Immuno Nuclear; Stillwater, Minnesota).¹ The assay was unaffected by addition of bilirubin. Concentrations of bilirubin, albumin, and creatinine and activities of alkaline phosphatase and alanine aminotransferase were measured in aliquots of the same samples. Samples were taken from all patients at the start of the study; a second sample was taken from all the patients except one, who died two months after the start of the study, and a third sample was taken from three patients. We monitored the clinical progression of the disease for 15 months or until death.

At the start of the study the plasma methionine enkephalin concentration (median 160 (range 50-1310) pmol/l) was significantly increased ($p<0.001$, Mann-Whitney U test) compared with the concentration that we had found in healthy people (65 (50-95) pmol/l) and in patients with other diseases (73 (50-110) pmol/l) in a previous study.¹ Median (range) values (and the limits of normal) of other plasma measurements in this study were: bilirubin 28 (8-367) $\mu\text{mol/l}$ (3-15 $\mu\text{mol/l}$); alkaline phosphatase 357 (147-1274) IU/l (21-91 IU/l); alanine aminotransferase 64 (21-169) IU/l (0-35 IU/l);

albumin 37 (26-45) g/l (37-49 g/l); and creatinine 75 (47-186) $\mu\text{mol/l}$ (45-120 $\mu\text{mol/l}$).

Spearman's rank correlation showed that methionine enkephalin concentration was significantly correlated with bilirubin concentration ($r=0.738$, $p<0.001$), alkaline phosphatase activity ($r=0.492$, $p<0.005$), and plasma albumin concentration ($r=-0.455$, $p<0.01$) but not with alanine aminotransferase activity or plasma creatinine concentration.

Seven patients died a median of 10 months (range 2-13 months) after the start of the study (figure). Three died from renal failure with ascites that was resistant to

Plasma methionine enkephalin concentrations in patients with primary biliary cirrhosis. Horizontal dotted line indicates upper limit of normal in healthy controls¹

*Patient died