nebuliser solution of ipratropium contains the preservative, benzyonium chloride, which can trigger airway constriction in some asthmatics¹. I would point out that in the UK ipratropium bromide nebuliser solution contains no preservative or stabilising agent and comes in the form of sterile unit dose vials. This has been the case since June 1987 and on 31st March 1988 the multi-dose ipratropium bromide formulation, which did contain the preservative benzalkonium chloride and EDTA, was discontinued. The reason for this change in the solution was so that the potential risk of preservative-induced paradoxical bronchoconstriction would be eliminated.

I would be most grateful if the opportunity arises, that this distinction between the formulation currently available in Canada and that available in the UK could be made in a subsequent issue.

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Reference

1. Hargreave, F.E. The drug treatment of asthma: how can it be better applied. *Postgrad Med J* 1988, **64** (Suppl. 4): 74–81.

Porphyria cutanea tarda and human immunodeficiency virus: two new cases

Sir,

Concerning the case presented by Ong *et al.*,¹ we report two more patients with porphyria cutanea tarda (PCT) associated with human immunodeficiency virus (HIV) infection.

Case 1

A 32 year old male with a background of intravenous drug addiction and heavy alcohol intake presented with a 2-year history of multiple blister-like lesions and small scars on the face and the back of his hands, cutaneous hyperpigmentation and facial hypertrichosis. Generalized lymphadenopathy and hepatomegaly were also observed. The most prominent laboratory results were: positive anti-HIV antibodies (ELISA); a lymphocyte count of $1.1 \times 10^9/l$, with 0.16×10^9 CD4 cells; alanine transaminase (SGPT) level of 52 IU/l (normal range: 0–35 IU/l); aspartate transaminase (SGOT) level of 65 IU/l (1–40 IU/l); gamma-glutamyl-transferase (GGT) of 117 IU/l (0–30 IU/l); plasma iron concentration was $19.5 \mu\text{mol/l}$ (12–26 $\mu\text{mol/l}$); transferrin, 47 $\mu\text{mol/l}$ (45–70 $\mu\text{mol/l}$); urine uroporphyrin, 343.2 nmol/day (<48 nmol/day); and coproporphyrin in urine, 1578 nmol/day (<300 nmol/day). The patient refused to continue the study.

Case 2

A 33 year old male intravenous drug addict and heavy drinker was hospitalized with fever, asthenia, weight loss, dysphagia and progressive dyspnoea of one month duration. He presented dark skin pigmentation, facial hypertrichosis and scars on face and hands, as well as oral candidiasis and

hepatomegaly. Radiography of the thorax revealed bilateral alveolar infiltrates. Laboratory results were as follows: positive anti-HIV antibodies (ELISA); lymphocyte count of $0.89 \times 10^9/l$; SGOT level of 117 IU/l; SGPT level of 49 IU/l; SGGT of 26 IU/l; lactate dehydrogenase (LDH) was >667 IU/l (normal range: 120–240 IU/l); serum iron concentration, 2.7 $\mu\text{mol/l}$; transferrin, 27 $\mu\text{mol/l}$; urine uroporphyrin, 836.4 nmol/day; and urine coproporphyrin, 480 nmol/day. In spite of antibiotic treatment, the patient died 20 days after admission secondary to consumption coagulopathy. Necropsy was not authorized.

The association of PCT with HIV infection has been described in four patients,^{1,2} to which we now add two new cases. All six were males belonging to different risk groups (two intravenous drug addicts, three homosexuals and one who admitted to having had sexual contact with a Central African prostitute), and reported varying degrees of alcoholic intake in the past. All developed symptomatic HIV infection (one, persistent generalized lymphadenopathy, and the remaining five, diverse infections included in group IV-C of the present classification of the Center for Disease Control in Atlanta). Four died after varying periods of time following diagnosis of PCT (ranging from 3 weeks to 6 years), one remains alive after 6 months, and we have no information regarding the status of our case 1.

Although it has been suggested that HIV or some associated opportunist agent might alter the porphyrin metabolism, interfering with the function of the cytochrome P-450 dependent mixed-function oxidase system,² this has not been proved. It is also difficult to assess the exact role of alcohol in the clinical expression of PCT in these patients.

We consider that the communication of new cases of this association will help to establish its true incidence and prognostic significance, as well as to stimulate the investigation of possible pathogenic mechanisms.

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References

1. Ong, E.L.C., Ellis, M.E., McDowell, D., Gebril, M., Weinkobe, C. & Ead, R. Porphyria cutanea tarda in association with the human immunodeficiency virus infection. *Postgrad Med J* 1988, **64**: 956–957.
2. Wissel, P.S., Sordillo, P., Anderson, K.E., Sassa, S., Savillo, R.L. & Kappas, A. Porphyria cutanea tarda associated with the acquired immune deficiency syndrome. *Am J Hematol* 1987, **25**: 107–113.

Renal and hepatic impairment in association with diclofenac administration

Sir,

We should like to report a case of renal and hepatic impairment following the administration of the non-steroidal anti-inflammatory drug diclofenac.

A 48 year old man was admitted with 2 week of malaise, anorexia and jaundice. He was hypertensive with occasional anginal pains, controlled by isosorbide and atenolol and chlorthalidone, and suffered from schizophrenia, which had been treated for many years by thioridazine. One month prior to admission he had been prescribed diclofenac for joint pains.

He was afebrile, dehydrated and jaundiced with palmar erythema but had no other stigmata of chronic liver disease. Blood pressure was 160/90 mmHg.

His liver function tests showed bilirubin of 141 $\mu\text{mol/l}$, raised transferases, alkaline phosphatase and gamma glutamyl transferase but normal coagulation screen. Renal function was impaired with a creatinine of 777 $\mu\text{mol/l}$. Blood and urine cultures were sterile. Autoantibody profile was normal and screening for leptospirosis, cytomegalovirus, Epstein-Barr virus, herpes zoster, hepatitis A and B were negative. Ultrasound showed normal sized kidneys without evidence of obstruction, normal liver texture and no bile duct dilation.

His diclofenac, isosorbide and thioridazine were withdrawn and he was rehydrated orally. Liver biopsy showed hepatitis with an inflammatory infiltrate including eosinophils consistent with a drug reaction. Renal biopsy revealed intense tubulo-interstitial inflammatory infiltrate, including numerous eosinophils, associated with degenerative changes in the tubular epithelial cells.

His liver function tests returned to normal and creatinine stabilized at 190 $\mu\text{mol/l}$.

Prostaglandins have only a minor role in normal kidney haemodynamics but are important in the autoregulation of renal blood flow under conditions of stress. Administration of non-steroidal anti-inflammatory agents to patients with impaired renal function may precipitate renal failure.^{1,2} In this case the patient had been well and another mechanism of damage needs to be postulated.

In common with other non-steroidal anti-inflammatory agents diclofenac has been reported in association with interstitial nephritis.³ This is a rare idiosyncratic reaction characterized by a predominantly T lymphocytic and eosinophilic infiltrate without evidence of antigen bound to tubular membrane.⁴⁻⁷

Hepatitis in association with non-steroidal anti-inflammatory drugs is rare and thought to be a hypersensitivity reaction, often with other organ involvement.⁸ Diclofenac has been linked to reversible abnormalities in liver function tests⁹ as well as being reported as a cause of acute hepatitis.¹⁰⁻¹² Some authors

favour an immunological mechanism of damage whilst others suggest production of toxic metabolites.

We believe that diclofenac was responsible for both the hepatitis and interstitial nephritis and that this is the first case report of hepato-renal damage due to this drug. Review of symptoms as well as liver and renal function of patients commenced on diclofenac is prudent medicine.

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References

1. Clive, D.M. & Stoff, J.S. Renal syndromes associated with non-steroidal anti-inflammatory drugs. *N Engl J Med* 1984, **310**: 563-572.
2. Carmichael, J. & Shankle, S.W. Effects of non-steroidal anti-inflammatory drugs on prostaglandins and renal function. *Am J Med* 1985, **78**: 992-1000.
3. Rossi, E., Ferraccioli, G.F., Menta, R., Dall'Aglio, P.P. & Migone, L. Diclofenac associated acute renal failure. *Nephrol* 1985, **40**: 491-493.
4. Reeves, W.B., Foley, R.J. & Weinman, E.J. Renal dysfunction from non-steroidal anti-inflammatory drugs. *Arch Int Med* 1984, **144**: 1943-1944.
5. Adams, D.H., Howie, A.J., Michael, J., McConkey, B., Bacon, P.A. & Adu, D. Non-steroidal anti-inflammatory drugs and renal failure. *Lancet* 1986, **i**: 57-60.
6. Finkelstein, A., Fraley, D.S., Stachura, I., Feldman, H.A., Gandy, D.R. & Bourk, E. Fenoprofen nephropathy: lipoid nephrosis and interstitial nephritis. *Am J Med* 1982, **72**: 81-87.
7. Bender, W.K., Whelton, A., Beschoner, W.E., Darwish, M.O., Hall-Craggs, M. & Solez, K. Interstitial nephritis, proteinuria and renal failure caused by non-steroidal anti-inflammatory drugs. *Am J Med* 1984, **76**: 1006-1012.
8. O'Brian, W.M. Adverse reactions to non-steroidal anti-inflammatory drugs. *Am J Med* 1986, **80** (Suppl 4B): 70-80.
9. Ciccolunghi, S.N., Chaudri, H.A., Schubiger, B.I. & Reddrop, R. Report on a long term tolerability study of up to two years with diclofenac sodium. *Scand J Rheumatol* 1978, **22**: 86-96.
10. Dunk, A.A., Walt, R.P., Jenkins, W.J. & Sherlock, S.S. Diclofenac induced hepatitis. *Br Med J* 1982, **284**: 1605-1606.
11. Breen, E.G., McNicholl, J., Cosgrove, E., McCabe, J. & Stevens, F.M. Fatal hepatitis associated with diclofenac. *Gut* 1986, **27**: 1390-1393.
12. Schapira, D., Bassan, L., Nahir, A.M. & Scharf, Y. Diclofenac induced hepatotoxicity. *Postgrad Med J* 1986, **62**: 63-65.