

Artificial colourings and adverse reactions

Drs L GRACEY-WHITMAN and S ELL (Queen Elizabeth Hospital, King's Lynn, Norfolk PE30 4ET) write: An 80 year old man with membranous glomerulonephritis was reviewed in clinic after an emergency admission in heart failure. His prednisolone, nizatidine, and amiloride were stopped, his frusemide was halved to 80 mg once daily, and his enalapril was increased from 5 mg to 10 mg once daily. One week later, he developed a widespread, pruritic maculopapular rash. The patient's wife (who had read the fine print of the data sheet) noted that enalapril in 10 mg and 20 mg preparations contains colouring agents, whereas 2.5 mg and 5 mg preparations do not. As her husband's symptoms were much improved with the higher dose of enalapril, she continued his treatment by giving him two 5 mg (colour free) tablets. The rash had resolved by his next monthly clinic appointment. He continues to tolerate enalapril, now 20 mg given once a day as four 5 mg tablets.

Shortly thereafter, a 74 year old woman presented with a painful, extensive eczematous rash. She said the rash had started two to three days after her enalapril dosage had been changed from 5 mg twice a day to a single 20 mg dose. When she was given four 5 mg tablets instead of one 20 mg tablet the rash resolved within three days.

The Medicines Control Agency's online information lists 1005 skin and subcutaneous tissue disorders associated with enalapril—about a fifth of the total adverse drug reactions recorded for this drug.¹ Enalapril is thought to be one of the least troublesome angiotensin converting enzyme inhibitors as it lacks the sulphhydryl group, which is thought to be responsible for the cutaneous side effects of some other angiotensin converting enzyme inhibitors. This begs the question: what caused the rash?

The colouring agent common to the 10 mg and 20 mg preparations of enalapril is mapico red; the 20 mg preparation also contains mapico yellow. Mapico red and mapico yellow are iron oxides; allergic reactions to these and to other colouring agents are common and well documented.¹ The 2.5 mg and 5 mg preparations are colour free.

In a recent case of bullous eruptions after changing from captopril to enalapril "for patient convenience," the authors could not explain the eruption.² The enalapril dose in that case was 10 mg, and we wonder if the bullous eruption was due to the colouring agent, as our two cases suggest. We conclude that not all adverse drug reactions are adverse reactions to the drug itself: a

colour free formulation should be tried before switching to another drug.

- Hanssen M. E for additives. Wellingborough, Northamptonshire: Thorsons, 1984.
- Mullins PD, Choudhury SL. Enalapril and bullous eruptions. *BMJ* 1994;309:1411.

Painful dysaesthesia with ciprofloxacin

Dr D ZEHNDER, Professor R HOIGNE, Professor K A NEFTEL, and Dr R SIEBER (Zieglerspital, 3001 Berne, Switzerland) write: Fluoroquinolones have been associated with various adverse effects.^{1,2} One case of peripheral neuropathy has been reported.³ We report two cases of generalised painful dysaesthesia due to ciprofloxacin, a reaction not previously associated with this particular fluoroquinolone.

A healthy 30 year old woman with a gynaecological infection was treated with oral ciprofloxacin 500 mg twice a day for six days. She experienced flu-like symptoms and headache, which disappeared immediately after discontinuation of ciprofloxacin. Two months later she was given ciprofloxacin to accompany hysterosalpingography. Within 30 minutes of taking the drug she reported flu-like symptoms, which developed into headache, tightness of breath, weakness, and dizziness. After 90 minutes painful dysaesthesia started in both legs, which peaked 90 minutes later. She felt a strong generalised musculoskeletal pain, which increased on walking. She took 1 g paracetamol and the pain subsided slightly. After two hours of sleep she felt weak and exhausted. All symptoms disappeared within nine hours with no evidence of muscle damage.

A 74 year old man was admitted with symptoms suggestive of a urinary tract infection. *Escherichia coli* was cultured in a urine sample. He was given intravenous ciprofloxacin (200 mg twice a day), with paracetamol and chloral hydrate as needed. Four days later epididymitis was confirmed by ultrasonography. Six days after admission he developed painful dysaesthesia, beginning in his head and rapidly spreading over the whole body and the legs. The pain peaked 10 hours after the last intravenous dose of ciprofloxacin and disappeared over the next 36 hours. Treatment was changed to oral ciprofloxacin (500 mg twice a day). No comparable symptoms were noted during the oral treatment.

Fluoroquinolones can cause various neurological symptoms. The manufacturers of ciprofloxacin had not received any previous reports of painful dysaesthesia after the drug.

- Davis H, McGoodwin E, Reed TG. Anaphylactoid reaction reported after treatment

with ciprofloxacin. *Ann Intern Med* 1989; 111:1041-3.

- Wolfson JS, Hooper DC. Overview of fluoroquinolone safety. *Am J Med* 1991;91(suppl 6A):153-61.
- Aoun M, Jacqy C, Debusscher L, Bron D, Leher M, Noel P, et al. Peripheral neuropathy associated with fluoroquinolones. *Lancet* 1992;340:127.

High fever induced by sulphasalazine

Drs S D HEARING, S PLAYFOR, and S J BENTLEY (Warrington Hospital, Warrington WA5 1QG) write: We report a case of high fever induced by sulphasalazine.

A 42 year old white woman with a two year history of rheumatoid arthritis presented with a high fever and constitutional illness. Ten days before admission she had started taking sulphasalazine 1 g twice daily as second line treatment. After three days of treatment she developed general malaise and sulphasalazine was stopped. On the day of presentation sulphasalazine treatment had been restarted at a dose of 1 g twice a day. After the second dose she became rapidly unwell and presented with a confirmed fever of 45°C. She had no history or family history of high fever with any drugs. Her only other drug treatment was piroxicam and ketoprofen, both taken intermittently to control symptoms. An adverse drug reaction was diagnosed since extensive investigation failed to disclose an alternative cause. Treatment with corticosteroids, paracetamol, and intravenous fluids was started and she fully recovered after four days.

Sulphasalazine has occasionally caused serious idiosyncratic side effects.^{1,3} Most side effects of sulphasalazine, however, are mild.⁴ A mild fever often occurs in patients taking sulphasalazine,¹ usually as part of a hypersensitivity reaction, with a rash and eosinophilia that resolve on withdrawal. Our patient's reaction was severe and more in keeping with the course of the neuroleptic malignant syndrome.⁵ The manufacturers have confirmed five other cases of severe fever in association with sulphasalazine treatment from a global database. Severe fever and constitutional illness are rare idiosyncratic side effects of sulphasalazine.

- Watkinson G. Sulphasalazine: a review of 40 years' experience. *Drugs* 1986;32(suppl 1): 1-11.
- Farr M, Scott DG, Bacon PA. Side effect profile of 200 patients with inflammatory arthritides treated with sulphasalazine. *Drugs* 1986;32(suppl 1):49-53.
- Donovan S, Hawley S, MacCarthy J, Scott DL. Tolerability of enteric coated sulphasalazine in rheumatoid arthritis. Results of a co-operating clinic study. *Br J Rheumatol* 1990;29:201-4.
- Amos RS, Pullar T, Bax DE, Situnayake D, Capell HA, McConkey B. Sulphasalazine for rheumatoid arthritis: toxicity in 774 patients monitored for one to 11 years. *BMJ* 1986; 293:420-3.
- Bristow MF, Kohen D. How "malignant" is the neuroleptic syndrome? *BMJ* 1993;307: 1223-4.

Angio-oedema associated with risperidone

Drs C COONEY and A NAGY (Psychiatric Unit, Barnet General Hospital, Barnet, Hertfordshire EN5 5QD) write: A 30 year old woman with a history of schizo-affective disorder was admitted to this psychiatric unit. She had been treated with a combination of intramuscular depot flupenthixol and oral thioridazine, and paroxetine treatment had been started two months previously. On admission she was receiving thioridazine 100 mg nightly and paroxetine 20 mg daily. She started taking risperidone, the dose being increased to 6 mg daily after three days. Two weeks later she developed facial and periorbital oedema. The dose was halved and the oedema subsequently subsided. Her mental state deteriorated, however, and the risperidone was increased to 6 mg daily. Within three days facial and periorbital oedema recurred. Risperidone was discontinued and the oedema resolved completely over two weeks. Biochemical and haematological screening gave normal results. Evaluation of the components of the complement system showed a low C4 concentration at 0.16 g/l (reference range 0.20-0.65 g/l),¹ and a normal C3 concentration at 0.84 g/l (reference range 0.75-1.65 g/l). Plasma concentration of C1 esterase inhibitor was low at 0.10 g/l (0.15-0.35 g/l); its function was also low (<50 000 U/l). This profile was replicated one month after the oedema had subsided, indicating that this was probably phenotypic of the patient rather than a reflection of the use of complement by the reaction itself. She had shown a similar reaction to lithium one year previously. In addition, her sister had a history of angio-oedema.

Risperidone is the first of a new group of antipsychotics, the benzisoxazoles.² To our knowledge, there are no reports of angio-oedema associated with the drug. The reappearance of angio-oedema on rechallenge is strong evidence implicating risperidone. The immunology investigations show a moderate defect of C1 esterase inhibitor concentrations or function, in this patient. Risperidone may have suppressed her already low C1 inhibitor activity, permitting the C4-C2 activation manifest in angio-oedema. We welcome comments from others who have had experience of similar reactions to psychotropic drugs.

- Ward AM. *PRU handbook of clinical immunology*. 4th ed. Sheffield: PRU Publications, 1993.
- Janssen PAJ, Niemegeers CJE, Awouters F, Schellekens KHL, Megens AAHP, Meert TF. Pharmacology of risperidone (R 64 7 6 6), a new antipsychotic with serotonin-2, and dopamine D2 antagonistic properties. *J Pharmacol Exp Ther* 1988;244: 685-93.