glaucoma. Its lipid solubility allows greater ocular penetration, so a therapeutic effect is achieved with a lower dose, and the high incidence of local and systemic side effects found with adrenaline may be avoided. Although some ocular side effects have been reported (conjunctival hyperaemia, tearing, and conjunctivitis), systemic side effects (palpitations, tremor, sweating, hypertension, and ventricular ectopics) have not been encountered.^{1,3} We describe two patients with controlled hypertension whose blood pressure rose significantly while they were using dipivalyl adrenaline for glaucoma.

A 70 year old woman taking hydralazine 50 mg twice a day and cyclopentiazide K two tablets daily had a mean blood pressure of 177/91 mm Hg before starting dipivalyl adrenaline therapy. While using dipivalyl adrenaline her blood pressure rose to a mean of 218/106 mm Hg ($p < 0.01$ systolic, $p < 0.1$ diastolic). After dipivalyl adrenaline was discontinued it fell to 182/95 mm Hg. A 56 year old woman had a mean blood pressure of 135/85 mm Hg on xipamide 20 mg daily. Two months after starting dipivalyl adrenaline her blood pressure rose and reached a mean of 183/103 mm Hg ($p < 0.05$) over four months of continued treatment; it fell to 150/90 mm Hg once the drug was stopped. In both cases blood pressure remained raised for four to six months while the patients were receiving dipivalyl adrenaline and returned to pretreatment levels two to four weeks after the drug was stopped. Dipivalyl adrenaline is used when topical β blockers might be dangerous and the miosis of pilocarpine inconvenient. It is considered to be free of systemic side effects. Although only two patients are reported, we think that it should be used with caution in patients receiving antihypertensive agents.

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2 Wandel T, Spinak M. Toxicity of dipivalyl epinephrine. *Ophthalmology* 1981;88:259-60.

3 Kerr CR, Hass I, Drance SM, Walters MB, Schulzer M. Cardiovascular effects of epinephrine and dipivalyl epinephrine applied topically to the eye in patients with glaucoma. *Br J Ophthalmol* 1982;66:109-14.

Hypoglycaemia induced by co-trimoxazole in AIDS

Drs A SCHATTNER, E RIMON, L GREEN, and R COSLOVSKY and Professor Z BENTWICH (Department of Medicine C, Kaplan Hospital and Hadassah Medical School, Rehovot 76100, Israel) write: In routine use co-trimoxazole seems to have little toxicity. When adverse effects do occur they usually include minor gastrointestinal or cutaneous reactions. Severe toxicity is unusual.¹ The ability of sulphonamides and co-trimoxazole to cause hypoglycaemia, particularly in conjunction with other facilitating factors, was recognised long ago, but hypoglycaemia associated with treatment with co-trimoxazole has been encountered only rarely.² We describe a patient with AIDS and *Pneumocystis carinii* pneumonia who had an episode of severe hypoglycaemia induced by co-trimoxazole. Neither our national drug monitoring centre nor the manufacturers of the drug have reported other cases of this side effect.

A 34 year old white homosexual man had been diagnosed as suffering from AIDS two years previously after developing weight loss, biopsy proved *P carinii* pneumonia, and Kaposi's sarcoma. He was also human immunodeficiency virus (HIV) positive and T4 cell depleted. He was taking co-trimoxazole twice daily when fever, generalised pruritus, and progressive weakness necessitated his admission.

The main new findings included pancytopenia with a hypocellular bone marrow, mild jaundice, hepatomegaly associated with the presence of hepatitis B core antibody, and a non-specific acute hepatitis seen in a liver biopsy specimen. His serum bilirubin concentration ranged from 34 to 82 $\mu\text{mol/l}$, alkaline phosphatase activity from 600 to 800 IU/ml, transaminase activity from 250 to 350 IU/ml, and his prothrombin time was 70% of the control value. He had oral candidiasis. The results of renal function tests were normal, and fasting plasma glucose and insulin concentrations on admission were 4.9 mmol/l and 6.3 mU/l respectively.

All drugs were stopped, and cultures of bronchoalveolar lavage fluid over seven days yielded negative results. The patient's temperature increased, however, and he developed dyspnoea associated with auscultatory and radiographic findings suggestive of recurrent

P carinii pneumonia. Intravenous co-trimoxazole was started and continued despite the appearance of a transient erythematous rash. No other drugs were administered concomitantly. Slight fasting hypoglycaemia developed on the fourth and fifth days of treatment (3.5 and 2.9 mmol/l respectively), but no action was taken. On the morning of the sixth day the patient fell off his bed and was found to be stuporous with no focal neurological signs. His plasma glucose concentration was 1.1 mmol/l, a simultaneous serum insulin concentration was 12 mU/l, with a raised C peptide concentration and a serum cortisol concentration of 340 $\mu\text{g/l}$.

Intravenous dextrose rapidly improved his neurological state, and there were no further episodes of hypoglycaemia over several months. Oral co-trimoxazole was started, and his fever settled and pulmonary state improved. The patient died five months later, and at necropsy no insulinoma or other tumour that might have been associated with his hypoglycaemia was found.

With the increasing use of co-trimoxazole to treat *P carinii* pneumonia in patients with AIDS a particularly high incidence of adverse reactions to the drug has been noted.^{1,4} Signs of drug toxicity may appear in as many as 78% of patients with AIDS and *P carinii* pneumonia,⁴ compared with about 8% in a general population.¹ The most common adverse reactions were rash, fever, cytopenias, and hepatotoxicity; but hypoglycaemia has not been reported to our knowledge. The reason for the high frequency of side effects to co-trimoxazole in AIDS remains obscure, but higher serum sulphamethoxazole concentrations in AIDS may be partly responsible.⁵ In our patient high drug concentrations were likely, and the hepatitis contributed to this. Liver disease may have also exacerbated the hypoglycaemia by impairing hepatic glycogenolysis and gluconeogenesis,⁶ but this cannot have been the predominant factor as hypoglycaemic episodes did not recur.

Hypoglycaemia induced by co-trimoxazole is a rare but recognised adverse effect. Sulphonamides have some chemical resemblance to oral hypoglycaemic agents. Sulphamethoxazole displaces sulphonylurea drugs from their binding protein and may potentiate their effects.⁷ Similarly binding of sulphamethoxazole to pancreatic islet tissue mimicking the effect of sulphonylureas and stimulating insulin release seems to be possible, though it has not been documented previously. The serum insulin concentrations of 12 mU/l were inappropriately high for a severe hypoglycaemia and support the above mechanism, in conjunction with the effects of poor nutrition and hepatic dysfunction that are also common with AIDS, making these patients more likely to develop hypoglycaemia.

With the growing number of patients with AIDS treated with high doses of co-trimoxazole this adverse reaction may occur more often. The potential of co-trimoxazole to cause hypoglycaemia should be more widely recognised, and patients should be monitored for the possible appearance of hypoglycaemia associated with sulphamethoxazole.

1 Jick H. Adverse reactions to trimethoprim-sulphamethoxazole in hospitalized patients. *Rev Infect Dis* 1982;4:426-8.

2 Poretzky L, Moses AC. Hypoglycemia associated with trimethoprim-sulphamethoxazole therapy. *Diabetes Care* 1984;7:508-9.

3 Small KB, Harris CA, Friedland GH, Klein RS. The treatment of *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. *Arch Intern Med* 1985;145:837-40.

4 Gordin FM, Simon GL, Wofsy CB, Mills J. Adverse reactions to trimethoprim-sulphamethoxazole in patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 1984;100:495-9.

5 Bowden FJ, Harman PJ, Lucas CR. Serum trimethoprim and sulphamethoxazole levels in AIDS. *Lancet* 1986;i:853.

6 Fischer KF, Lees JA, Newman JH. Hypoglycemia in hospitalized patients. Causes and outcomes. *N Engl J Med* 1986;315:1245-50.

7 Baciewicz AM, Swafford WB Jr. Hypoglycemia induced by the interaction of chlorpropamide and co-trimoxazole. *Drug Intell Clin Pharm* 1984;18:309-10.

Acute painful proximal myopathy associated with nalidixic acid

Drs ANDREW J CARMICHAEL and ANTHONY M MARTIN (Renal Unit, Royal Infirmary, Sunderland SR2 7JE) write: Several drugs are known to cause myopathies, including an acute painful proximal myopathy,¹ but we are unaware of any reports implicating nalidixic acid.

A 53 year old woman with chronic pyelonephritis, controlled hypertension, and impaired renal function (urea 29 mmol/l, creatinine 345 $\mu\text{mol/l}$) was prescribed

full dose nalidixic acid (Negram) 1 g four times a day for a urinary tract infection. She had never received this antibiotic previously. Within 24 hours of starting treatment she developed severe aching and weakness in the proximal muscles of the arms and legs. She stopped the treatment after taking four doses and her symptoms gradually resolved over the next three days. Her only concomitant therapy was amiloride hydrochloride and hydrochlorothiazide (Moduretic) two tablets a day, which she had taken regularly for two years, and this was continued. Serum potassium concentration was normal.

The Committee on Safety of Medicines has received five reports of myalgia associated with nalidixic acid (personal communication) and the Australian Drug Evaluation Committee a further three.² Given the strong temporal relation between the myopathy and nalidixic acid treatment in our patient and the substantial number of suspected reports, we think it would be appropriate to include nalidixic acid in the list of drugs capable of inducing a painful proximal myopathy. We also advocate adherence to the manufacturer's recommendation to reduce the dose in renal impairment, which may have contributed to this adverse reaction.

1 Lane RJM, Mastaglia FL. Drug induced myopathies in man. *Lancet* 1978;ii:562-5.

2 Anonymous. Adverse effects of drugs commonly used in the treatment of urinary tract infections: report from the Australian Drug Evaluation Committee. *Med J Aust* 1972;i:435-8.

Severe salt and water deficiency associated with a combination of atenolol and chlorthalidone

Drs CHRISTINE A BOWMAN and WILLIAM J JEFFCOATE (City Hospital, Nottingham NG5 1PB) write: Professor W J MacLennan (4 June, p 1551) discussed the electrolyte imbalances that may arise in elderly people taking diuretics. Such disturbances have not been reported previously in patients on low dose combinations of a β blocker and a thiazide. We describe a case of severe salt and water deficiency in a patient with carcinoma of the bronchus in whom a combination of atenolol 50 mg and chlorthalidone 12.5 mg was thought to be the cause.

A previously healthy 75 year old woman presented with an eight week history of cough, breathlessness, blackouts, and malaise. She had no past or recent symptoms of gastrointestinal or renal disturbances. She had received a 14 day course of the combination of atenolol and chlorthalidone, one tablet daily, until two days before admission, and seven 5 mg tablets of prochlorperazine in the week before admission (for "dizziness").

She was dehydrated, and her blood pressure was 110/60 mm Hg lying and 80/40 mm Hg sitting. Plasma electrolyte concentrations were: sodium 109 mmol/l, potassium 1.5 mmol/l, urea 6.8 mmol/l, and creatinine 51 mmol/l. After partial rehydration with 1.5 litres of isotonic saline and 121.5 mmol potassium chloride/l intravenously her plasma sodium and potassium concentrations were 118 and 2.4 mmol/l respectively, and osmolality was 259 mmol/kg. Simultaneous urinary values were 94 and 26 mmol/l and 532 mmol/kg. Calcium and glucose concentrations were normal.

A bronchoscopic biopsy specimen of a hilar mass showed small cell anaplastic carcinoma. After full rehydration over 27 days ectopic adrenocorticotrophic hormone secretion and adrenocortical insufficiency were excluded. Neither clinical nor biochemical electrolyte disturbance recurred during the remaining four months of her life, even though she received no further treatment.

The only known precipitating factor for the hypokalaemia was the short course of treatment with a low dose of chlorthalidone. Hypokalaemic tubular damage could have accounted for her severe salt and water loss, although inappropriate secretion of anti-diuretic hormone may have contributed to her low serum osmolality as a secondary effect. Chlorthalidone has been reported to cause hypokalaemia, either alone or in combination with atenolol,^{1,2} but the low dose, brief exposure, and severity of electrolyte disturbance in this case suggest either an idiosyncratic response or a previously unrecognised susceptibility secondary to underlying malignancy.

1 Scott A. Hazards of combined beta blocker/diuretic tablets. *Lancet* 1985;i:1395.

2 Walters EG, Horswill CE, Shetton JR, Akbau FA. Hazards of combined beta blocker/diuretic tablets. *Lancet* 1985;iii:220-1.