mental state examination he scored 17 out of a possible 30.

Postoperative delerium was diagnosed and the cefazolin discontinued; within 24 hours his mental state had improved sufficiently to allow discharge. All other medications were continued, save for the haloperidol, which was no longer required. Psychiatric follow up at one week confirmed complete resolution of his delerium.

Published reports cite neuropsychiatric symptoms developing with several of the cephalosporins —notably, cefuroxime and cephalexin,[1] cephalothin and cephaloridine,[1,2] and cephacetrile, ceftazidime, and cefazolin.[3] The health protection branch of Health and Welfare Canada, as well as one of the Canadian manufacturers of cefazolin, each lists two putative cases, though the evidence is anecdotal only (personal communication). This patient presented with classical changes in consciousness and mentation of a delerium or acute confusional state. While postcardiotomy delerium occurs in up to 28% of patients,[4] it tends to be brief and responds well to low dose haloperidol and reorientation in a quiet environment. As other organic causes had been adequately ruled out and there was no evidence of a functional aetiology we thought an adverse drug reaction was the most likely cause and cefazolin the most likely offending agent. Though it had been interrupted earlier in this man's postoperative course, it was the only agent present from the onset of his confusion and thus was at least a potentiating, if not an initiating, factor. Within 24 hours of the drug being stopped his mental state cleared remarkably, consistent with the observation of Vincken.[1]

Though the incidence of acute confusion with cephalosporins is likely to be small, and in this case the benefits of treating the postoperative fever vastly outweighed the risks, the case reminds us that adverse drug reactions should be high on the list of differential diagnoses in the acutely confused patient.

1 Vincken W. Psychotic reaction with cefuroxime. *Lancet* 1984; i:965.
2 Norrby SR. Side effects of cephalosporins. *Drugs* 1987;**34**(suppl 2): 105-20.
3 Geyer J, Hoffler D, Demers HG, Neimeyer R. Cephalosporin-induced encephalopathy in uremic patients. *Nephron* 1988; **48**:237.
4 Kornfeld DS, Heller SS, Frank KA, Edie RN, Barsa J. Delerium after coronary artery bypass surgery. *J Thorac Cardiovasc Surg* 1978;**76**:93-6.

Arthralgia associated with captopril

Drs S D H MALNICK and A SCHATTNER (Department of Medicine C, Kaplan Hospital, 76100 Rehovot, Israel) write:

Following the report of pseudopolymyalgia rheumatica associated with enalapril[1] we report a case of severe polyarthralgia and a false positive Venereal Disease Research Laboratory test result associated with captopril.

A 54 year old man was being treated with atenolol for hypertension, but after showing mildly disturbed lung function he was given captopril instead. Several days after treatment with captopril was started the patient experienced a migratory arthralgia in the metacarpophalangeal joints and wrists. After a month he experienced a severe arthralgia in the left hip, which he noted increased in severity one to two hours after he took the captopril tablets. Physical examination showed a considerable reduction in the mobility of the left hip with no local erythema or heat. A radiograph of the hip was normal. Laboratory investigations showed an erythrocyte sedimentation rate of 30 mm in the first hour and normal full blood count, glucose and electrolyte concentrations, and liver function values. Serological tests showed negative results of Rose-Waaler, latex, and antinuclear factor tests and normal concentrations of complement. A false positive result on the Venereal Disease Research Laboratory test was, however, found. Treatment with captopril was stopped and the patient received diclofenac and subsequently naproxen. Two weeks later he was entirely asymptomatic and the false positive result was no longer present. The patient declined rechallenge with captopril.

There have been reports of a serum sickness like syndrome with arthralgia, rash, and membranous glomerulopathy that resolved in two weeks.[2] Urticaria with arthralgia that resolved on withdrawal of captopril has also been described,[3,4] but a false positive Venereal Disease Research Laboratory test result has not been associated with captopril. The mechanism for this effect is unclear, but captopril has a similar structure and metabolite profile to penicillamine.[5] We suggest that the prevalence of "silent" autoantibodies in the serum of patients receiving captopril should be determined[6] and that captopril may rarely cause a drug induced autoimmune disorder in susceptible individuals.

1 Leloet X, Moore N, Deshages P. Pseudopolymyalgia rheumatica during treatment with enalapril. *Br Med J* 1989;**298**:325.
2 Hoorntje SJ, Ween JJ, Kallenberg CGM, *et al.* Serum sickness-like syndrome with membranous glomerulopathy in patient on captopril. *Lancet* 1989;ii:1297.
3 Smit AJ, Van der Laan S, DeMonchy J, *et al.* Cutaneous reactions to captopril—predictive value of skin tests. *Clin Allergy* 1984;**14**:413-9.
4 Luderer JR, Lookingbill DP, Schneck DW, *et al.* Captopril-induced skin reactions. *J Clin Pharmacol* 1982;**22**:151-9.
5 Dixon JS, Bird HA, Martin MFR, *et al.* Biochemical and clinical changes occurring during the treatment of rheumatoid arthritis with novel anti-rheumatoid drugs. *Int J Clin Pharmacol Res* 1985;5:25-33.
6 Schattner A. The origin of autoantibodies. *Immunol Lett* 1987; **14**:143-53.

Early renal artery occlusion after enalapril in atheromatous renal artery stenosis

Drs J MAIN and R WILKINSON (Renal Unit, Freeman Hospital, Newcastle upon Tyne) write:

Reversible renal failure is a well known side effect of angiotensin converting enzyme inhibitors in patients with severe renovascular disease. Renal artery occlusion associated with the use of angiotensin converting enzyme inhibitors has been reported,[1-5] but we report a further case with important differences from the previous ones.

Over six months difficulty was experienced in controlling the blood pressure of a 71 year old woman who was an ex-smoker. Initial treatment included captopril and was associated with a pronounced fall in blood pressure and a rise in plasma creatinine concentration from 153 to 222 μmol/l over three weeks. Captopril was stopped and creatinine fell gradually to 135 μmol/l in association with loss of blood pressure control. Intravenous urography showed a normal left kidney and a small right kidney with a faint but persistent nephrogram. The patient was treated with various combinations of nifedipine, methyldopa, frusemide, and prazosin, and plasma creatinine fluctuated between 133 and 210 μmol/l. After she developed clinical and radiographic features of pulmonary oedema and side effects of higher doses of prazosin and frusemide treatment was replaced by enalapril 2·5 mg daily, increased after three days to 5 mg with the addition of bumetanide 1 mg/day. Six days after starting enalapril the patient became anuric and developed acute pulmonary oedema. She reported no symptoms of hypotension, and the lowest recorded blood pressure after enalapril was started was 140/70 mm Hg. Despite a good symptomatic response to intravenous diamorphine, frusemide, and isosorbide dinitrate she remained anuric over the next 12 hours. A return of symptomatic pulmonary oedema was successfully treated with the removal of 2 litres of fluid in three hours by arteriovenous haemofiltration. Urgent arteriography showed occlusion of the right renal artery and a stenosis of the left renal artery with a distal occluding thrombus. It proved impossible to pass a guidewire through this obstruction despite infusion of streptokinase into the artery. The patient was not fit for surgery, and regular haemodialysis was started. After 10 days she suffered a cardiac arrest and died. Necropsy confirmed the presence of an atheromatous stenosis and recent occlusive thrombus in the left renal artery.

In four reports of six patients developing renal artery occlusion in association with angiotensin converting enzyme inhibitor treatment in native kidneys[1-4] the occlusions were discovered several months after treatment started. In each case there was a non-affected kidney, and the diagnosis was made by arteriography. In the one case with a close temporal association[5] the renal artery thrombosis was attributed to profound hypotension which developed three hours after the first dose of captopril. The important differences in our case were the close temporal association and the absence of hypotension.

It is, of course, possible that renal artery occlusion after several months' treatment simply represented the natural course of the disease, but the close temporal association in our case makes it more likely that the drug was responsible. Tillman *et al* have suggested that angiotensin converting enzyme inhibitors should be used for one month before definitive treatment in this group of patients,[4] so the occurrence of early occlusion is important.

We cannot be sure that this patient did not have an unrecorded asymptomatic hypotensive episode, but the development of pulmonary oedema quickly after the onset of anuria suggests that she was not hypovolaemic at the time of renal artery thrombosis. The ease of removal of 2 litres of fluid by haemofiltration without hypotension supported the absence of hypovolaemia.

In this patient previous exposure to angiotensin converting enzyme inhibitors had produced only a modest rise in plasma creatinine concentration. We have found that the effect of angiotensin converting enzyme inhibitors in patients with radiographically severe renal artery stenosis is variable, ranging from undetectable to rapid complete loss of function. In such patients renal function may diminish if blood pressure falls below a certain level, and this may explain the fluctuations in renal function seen in this patient during treatment with other drugs. The possibility of bilateral renal artery stenosis was considered, but we had thought that careful monitoring of creatinine concentrations would be sufficient precaution when enalapril was introduced. If angiotensin converting enzyme inhibitors can produce renal artery occlusion then clearly such an approach is not safe, and these drugs should be avoided in all patients in whom atheromatous renal artery stenosis is likely. This is a sizable group, including all hypertensive patients with evidence of vascular disease elsewhere or with any undiagnosed impairment of renal function.

The Committee on Safety of Medicines does not have a distinct category for renal artery occlusion, but the manufacturers are aware of three previous reports with enalapril (M Walters, Merck, Sharp & Dohme Ltd, personal communication).[2-4]

1 Hoefnagels WHL, Thien T. Renal artery occlusion in patients with renovascular hypertension treated with captopril. *Br Med J* 1986;**292**:24-5.
2 Hartnell GG, Allison DJ. Renal artery occlusion in patients with renovascular hypertension treated with captopril. *Br Med J* 1986;**292**:410.
3 Khalife K, Juilliere Y, Zannad F. Stenose bilaterale de l'artere renale aparue sous enalapril sans deterioration de la fonction renale. *Therapie* 1985;**40**:481.
4 Tillman DM, Malatino LS, Cumming AMM, *et al.* Enalapril in hypertension with renal artery stenosis: long-term follow-up and effects on renal function. *J Hypertension* 1984;**2**(suppl 2):93-100.
5 Williams PS, Hendy MS, Ackrill P. Captopril-induced acute renal artery thrombosis and persistent anuria in a patient with documented pre-existing renal artery stenosis and renal failure. *Postgrad Med J* 1984;**60**:561-3.