That the efferent limb of the "clubbing reflex" may be humoral is suggested by observations of hormonal factors being associated with clubbing. Patients with bronchial carcinoma and hypertrophic pulmonary osteoarthropathy have been reported to have raised concentrations of growth hormone.³ Clubbing has also been described in association with a case of thyroid carcinoma and primary hyperparathyroidism.⁴ Lam *et al* reported two cases (in brothers) with pachydermatoperiostosis, hypertrophic gastropathy, and complicated duodenal ulcers.⁵ In these cases the serum concentrations of gastrin were normal but concentrations of pepsinogen 1 and 2 were raised.

The clubbing associated with the Zollinger-Ellison syndrome in our patient, which regressed after resection of the tumour, was probably due to some substance produced by the tumour. Gastrin itself was unlikely to be the substance, as vagotomy, which may abolish clubbing, is often associated with raised serum concentrations of gastrin. Moreover, tumours such as gastrinomas, which are from the APUD cell series, are known to secrete many peptides, only some of which have been characterised.

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Neuropsychiatric complications related to use of prazosin in patients with renal failure

Although postural hypotension and syncope are well known side effects of prazosin, neuropsychiatric complications have rarely been recorded. We report on three neuropsychiatric patients who recovered completely after the drug was withdrawn.

Case reports

Case 1—A 63 year old housewife who had been receiving continuous ambulatory peritoneal dialysis for one year for diabetic renal failure was admitted because of impaired drainage of peritoneal dialysate. She also had hypertension, diabetic retinopathy, and peripheral and autonomic neuropathy. Her blood pressure was not well controlled despite treatment with metoprolol, and prazosin was started and increased to 2 mg three times daily. Over the next four weeks she became confused and suffered from visual hallucinations and paranoid ideas. No significant biochemical changes occurred, however, and her autonomic dysfunction did not change. An electroencephalogram showed intermittent diffuse slow wave abnormality, which was consistent with metabolic encephalopathy. Prazosin was stopped, and she recovered over eight weeks.

Case 2—A 70 year old woman with a 15 year history of diabetes mellitus stabilised by glibenclamide was admitted after three weeks of intermittent drowsiness, confusion, and uninhibited behaviour such as undressing. She also had longstanding hypertension, treated initially with methyldopa, but prazosin 5 mg three times daily had been started six weeks previously for better control. Over the past year she had developed diabetic renal failure, with urea concentration 19.6 (normal 3-8) mmol/l (117.6 (18-48) mg/100 ml) and creatinine concentration 280 (50-120) µmol/l (3.17 (0.57-1.36) mg/100 ml). She was afebrile and had no focal neurological deficit. There was no evidence of hypoglycaemia or postural hypotension, and cerebrospinal fluid composition and results of other biochemical investigations were normal. Over the next few days her mental state fluctuated, and an electroencephalogram was performed, which showed diffusely abnormal trace with no focal features. We suspected that this might be related to prazosin, which was stopped over the next three days; her mental state improved dramatically. Two months after discharge her mental state and behaviour were normal, and a repeat electroencephalogram showed great improvement.

Case 3—A 40 year old man with a 20 year history of insulin dependent diabetes and hypertension was admitted because of sudden left hemiparesis. Computed tomography of his head showed a lacunar infarct in the right internal capsule. While in hospital he had two grand mal seizures, controlled with phenytoin.

Prazosin 2 mg three times daily was also started because his blood pressure was not well controlled with methyldopa alone. His hemiparesis improved gradually and he returned home. He was readmitted two weeks later, however, because of psychotic behaviour. He was paranoid, with signs of organic psychosis, strong delusions of grandeur, and hallucinations. There was no biochemical evidence of hypoglycaemia or phenytoin toxicity, and an electroencephalogram showed intermittent slow waves over the right hemisphere, compatible with the vascular lesion. His renal function was mildly impaired, but it remained stable throughout his psychosis. Prazosin was stopped and the hypertension controlled with metoprolol. The psychosis was settled with a short course of chlorpromazine and trifluoperazine. Eight months after discharge and withdrawal of the major tranquilliser paranoia had not recurred.

Comment

We think that the increased abnormalities in the central nervous system in our three patients were due to prazosin, because their chronic renal failure might have affected the clearance of prazosin.

The results of pharmacokinetic studies in chronic renal failure are not yet consistent,^{1,2} though the 50% increase in the free fraction of prazosin observed in patients with chronic renal failure³ might explain the apparent association of central nervous system toxicity with renal failure. Animal studies also support the observation that prazosin could be responsible for the abnormal symptoms of the central nervous system.^{4,5}

We advise the cautious use of prazosin in patients with renal failure. The Committee on Safety of Medicines and the drug manufacturer have told us about one notification of paranoia and five of hallucination since 1974.

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Epidural methadone for preoperative analgesia in patients with proximal femoral fractures

Proximal femoral fracture in elderly patients is one of the most common fractures seen in the orthopaedic department. The treatment of choice is internal fixation, and a delay in performing the operation or contraindication to surgery creates problems in the nursing of patients. The optimal time for preoperative assessment, preparation, and medical stabilisation of these patients is about 12 to 24 hours.¹ Before and after surgery such patients are prone to pain, pressure sores, pneumonia, thromboembolic phenomena, and central depression caused by systemic narcotics.

Epidural analgesia induced by opiates is an accepted method of pain relief after surgical orthopaedic intervention.² Epidural methadone has the same analgesic potency as morphine but fewer complications; urinary retention is rarely seen, and respiratory depression has not been reported. We evaluated prospectively the effect of continuous epidural analgesia induced by methadone in patients with fractures of the femoral neck.

Patients, methods, and results

Twelve patients (seven women and five men, age range 21-93 (mean 68.9)) sustained proximal femoral fractures and were treated surgically by hemiarthroplasty or Richard's sliding compression nail. Epidural analgesia was started soon after clinical and radiological evaluation in the emergency room. We added 4 ml of methadone hydrochloride 0.1% to 6 ml of saline and injected this through the epidural catheter. The severity of the pain was evaluated subjectively before and two hours after the injection as follows: no pain=0, mild pain=1, and severe