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Fatal cardiac failure after a single dose of doxorubicin in myeloma-associated cardiac amyloid

Sir,
While the cardiotoxic effects of cumulative doses of doxorubicin are well recognized,^{1,2} the potential that this drug has for causing acute cardiac dysfunction is less well recognized. This is likely to be particularly important where there is pre-existing cardiac disease. We report a case where exposure to a single dose of doxorubicin resulted in fatal deterioration in cardiac function.

A 53 year old male presented with nephrotic syndrome and was found to have lambda light chain myeloma. Renal biopsy showed amyloid. Before treatment was started he developed acute pancreatitis which was complicated by renal impairment and severe fluid overload, with radiological evidence of pulmonary oedema. At this time blood pressure was 90/60 mmHg; electrocardiography showed low voltage complexes. Calculated echocardiographic ejection fraction was 47%; there was evidence of septal thickening (1.9 cm) but no chamber dilatation and no evidence of valvular disease or tamponade. Machine haemofiltration was instituted with correction of fluid overload and good biochemical control: there was no cardiovascular instability despite fluid removal of up to 3 kg per treatment. Five days later, treatment with doxorubicin 9 mg/m², vincristine 0.4 mg, and methylprednisolone 1 g/m² was given. Twenty-four hours after the initial dose he became hypotensive (70/50 mmHg) despite adequate filling pressures. Thermodilution cardiac output was 5.5 l/min despite treatment with dobutamine 28 µg/kg/min. Despite addition of adrenaline, dopamine, and enoximone there was continued haemodynamic deterioration and cardiac arrest occurred 4 h after transfer. At post mortem there was extensive amyloidosis involving the liver, spleen, kidneys and heart. The coronary arteries were patent and there was no evidence of infarction.

There are 3 previously published cases of fatal cardiac failure after low dose anthracycline administration; one case of fatal cardiac failure without evidence of coronary disease after 3 × 70 mg/m² daunorubicin (total dose 420 mg),³ and 2 cases of fatal cardiac failure following 50 mg and 80 mg; one of these patients had pre-existing coronary disease.⁴ In addition, there is one report of non-fatal myocardial infarction following each of 2 doses of doxorubicin⁵ although this is not the usual mechanism of anthracycline cardiotoxicity. In the present case there was no evidence of ischaemic heart disease or sepsis and the patient was stable although hypotensive until the drug was administered. We conclude that doxorubicin toxicity, superimposed on pre-existing cardiac impairment caused

by amyloidosis, was responsible for the patient's death. Caution is required in the administration of anthracyclines to patients where there is pre-existing myocardial disease. This has particular relevance to myeloma, where, as in this case, cardiac amyloid is a potential complication.

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Intra-operative bumetanide in cadaveric renal transplants

Sir,

In cadaveric renal transplants, one aims to achieve primary function with diuresis on restoring the circulation, to make post-operative management much easier and obviate the need for dialysis. According to our protocol, a central venous pressure (CVP) line is placed in each recipient and intra-operatively they receive cyclosporine A infusion (2.5 mg/kg), methylprednisolone (15 mg/kg) and 100 ml of 10% mannitol. CVP is maintained between 10–15 cm of water. Following the revascularization of the graft, we hope to see diuresis within 5–10 min. If this does not occur, we have been encouraged by the use of intravenous bumetanide (2 mg) as a bolus. This has resulted in immediate diuresis and continued primary function of the graft in 6 patients.

Bumetanide is a potent 'high-ceiling' diuretic with a number of features which make it desirable for use in renal transplant patients. After intravenous injection, the diuresis starts within a few minutes with sharp peak and short duration of action.^{1,2} The principal site of action is the thick ascending limb of Henle's loop where it inhibits the active reabsorption of Na⁺ and Cl⁻. There is evidence to suggest that it also has minor action at the proximal tubules via carbonic anhydrase inhibition. Bumetanide enhances glomerular filtration rate and renal plasma flow

independent of the diuretic and naturetic response. This vasodilator action is probably mediated by local prostaglandins, kinin and kallikrein activity.³ Pharmacologically, bumetanide is 40-fold more potent than frusemide on a weight for weight basis. The K^+ losses are less with bumetanide.

The role of bumetanide is acute pulmonary odema and congestive heart failure is well established. Bailey⁴ has described the use of bumetanide in 10 patients 2 months after their renal transplants and no serious side effects or biochemical abnormalities occurred. As far as we are aware, this is the only documented report of the use of bumetanide in renal transplant patients. We recommend its use at an early stage in the cadaveric renal transplants to obtain diuresis.

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Pseudo-obstruction secondary to anticholinergic drugs in Parkinson's disease

Sir,

We would like to report a case of pseudo-obstruction in a patient with Parkinson's disease who was taking lofepramine and oxybutinin. Neither drug has been reported to cause this complication, and thus this case illustrates the difficulty in treating patients with Parkinson's disease with anti-cholinergic drugs.

A 60 year old man with a 12 year history of Parkinson's disease, presented with urinary frequency, incomplete voiding, and increasing depression. The main features of his Parkinson's disease were rigidity, marked dyskinesias, severe 'on-off' fluctuations and constipation. Drugs on admission were cocareldopa, co-beneldopa, subcutaneous apomorphine as required, domperidone, lactulose, frusemide, digoxin, nifedipine and aspirin.

Videocystometry showed an unstable bladder for which he was treated with oxybutinin 5 mg twice a day and 10 mg at night.

Lofepramine was started 3 days later, at a dose of 70 mg at night, for depression. Three days after this, the patient went into acute urinary retention and needed catheterization. The oxybutinin and lofepramine were stopped. Twelve hours later he was found to be hypotensive and oliguric. On examination the abdomen was distended and tender, bowel sounds were absent and the rectum was empty. Abdominal radiographs showed dilated large and small bowel, with air throughout the bowel. A single contrast barium enema showed free flow up to the caecum. Amylase, sodium and potassium were normal.

A diagnosis of pseudo-obstruction was made and treatment was conservative consisting of intravenous fluids and a nasogastric tube. After 5 days he had made a full recovery. All previous medication except the lofepramine and oxybutinin were reintroduced without recurrence of the pseudo-obstruction.

The temporal relationship between the administration of lofepramine and oxybutinin and the bowel obstruction strongly suggests that one or both drugs played a pathogenic role. It is of interest that lofepramine is widely thought of as having markedly less anti-cholinergic side effects than other tricyclic antidepressants.¹ Nevertheless, all anti-cholinergic drugs produce smooth muscle relaxation which leads to bowel stasis and therefore may predispose to pseudo-obstruction. This is a relatively rare complication and is usually an idiosyncratic reaction.

Megacolon and dilatation of the small bowel have been described in patients with Parkinson's disease not taking anticholinergic medication.² Contributory factors in parkinsonian patients include disordered gut motility with generalized hypokinesia, delayed gastric emptying aggravated by levodopa,³ autonomic dysfunction and aggravation of constipation by anismus.⁴ Furthermore, Kupsky *et al.*⁵ have shown the presence of Lewy inclusion bodies in myenteric plexus ganglion cells in the oesophagus and colon in a patient with megacolon and Parkinson's disease. This may reflect primary involvement of the enteric nervous system by degenerative processes in Parkinson's disease. Thus, it can be seen that disturbances of alimentary function are a prominent feature in patients with Parkinson's disease and may make these patients particularly vulnerable to the effects of anti-cholinergic drugs on the bowel.

This case therefore illustrates the difficulty in treating patients with Parkinson's disease with anticholinergic drugs. Particular care is advised, when prescribing them to patients with Parkinson's disease.

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