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Antibiotics and Acute Renal Failure in Children with Cystic Fibrosis

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Children with cystic fibrosis (CF) are treated with a large number of potentially nephrotoxic medications yet the incidence of renal failure is rare. The risk of nephrotoxicity with aminoglycosides is well appreciated and current CF guidelines suggest trough and peak levels should be monitored after the third or fourth dose, and then weekly with baseline renal function checked at the start of therapy.

We recently treated three children with CF and acute renal failure all of whom had received gentamicin and ceftazidime in combination with other medication. Two children had a renal biopsy which showed acute tubular necrosis with additional interstitial nephritis in one. The patients required short term haemodialysis and recovered renal function. With other recently reported cases of CF and acute renal failure we would suggest that CF guidelines need to be amended to include monitoring of creatinine at the same times as gentamicin levels, particularly when combinations of antibiotics are being used or other risk factors are present.

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Introduction

Children with cystic fibrosis (CF) are often treated with aminoglycosides in combination with other antibiotics for pulmonary infections due to *Pseudomonas aeruginosa*[1]. For pharmacokinetic reasons, higher doses of aminoglycosides may be used in CF patients and prolonged treatment may be needed in view of the chronic nature of infection. Although the nephrotoxicity of aminoglycosides is well appreciated the incidence of renal failure in this group of patients appears to be a rare event[1]. However, our recent experience suggests the monitoring of renal function in patients on combined therapy needs to be modified. Three children with CF and acute renal failure were recently referred to our unit and required short-term haemodialysis.

Case 1

A 12-year-old boy commenced IV ceftazidime 125 mg/kg/day and gentamicin 6 mg/kg/day, both in three divided doses for infective exacerbation of his CF. Other medications included flucloxacillin, salmeterol, ursodeoxycholic acid, nasal fluticasone and multivitamins. Plasma creatinine was 70 µmol/l and after two days gentamicin dosage was increased to 7.6 mg/kg/day in view of a low peak serum level (2.4 mg/l). Ten days later he was readmitted with a four day history of diarrhoea and vomiting and the creatinine had risen to 187 µmol/l. A trough gentamicin level was 5.9 mg/l. Gentamicin was discontinued and one day later a random level was 3.5 mg/l. Creatinine had risen to 473 µmol/l.

Ultrasound revealed a single enlarged kidney with generalised increase in renal cortical echogenicity but preservation of cortical medullary differentiation. Biopsy showed extensive tubular necrosis.

Haemodialysis was initiated following a rise in the creatinine to 1104 µmol/l (18 days after start of antibiotics) and was maintained for one week. The urine output gradually improved and follow up creatinine was 75 µmol/l at the referral unit.

Case 2

A 5-year-old girl was admitted with CF and a wet cough despite three months oral ciprofloxacin and nebulised colistin. Her other drugs were salbutamol, fluticasone, multivitamins and pancreatic enzyme supplements. Intravenous ceftazidime 150 mg/kg/day and gentamicin 12 mg/kg/day both divided into three doses were commenced with flucloxacillin orally. There was a history of left hydronephrosis antenatally and a left pyeloplasty, performed at 2 years of age. Initial plasma creatinine was normal. After one week, the dose of gentamicin was increased to 13.5 mg/kg/day because of a peak serum level of 6.2 mg/l. At two weeks the peak gentamicin level was 12.8 mg/l and the dose reduced to 11 mg/kg/day. Nineteen days after commencing treatment her creatinine was noted to be 164 µmol/l and her gentamicin was discontinued. She was transferred to our care on day 22 and ultrasound revealed normal-sized kidneys with moderate hyperechoic parenchyma. In view of a persistently high random gentamicin levels of 5.4 mg/l, oliguria and a creatinine of 647 µmol/l, haemodialysis was undertaken for five days. Biopsy showed interstitial nephritis with florid features of acute tubular necrosis. Prednisolone treatment was given for five days, renal function gradually improved and follow up creatinine was 58 µmol/l.

Case 3

A 3-year-old boy with CF and severe gastro-oesophageal reflux was admitted for IV antibiotics in preparation for a fundoplication procedure. Other medications included cisapride, omeprazole, colistin, fluticasone, salmeterol, salbutamol, multivitamins, vitamin E and pancreatic enzyme supplements. He was treated with gentamicin 11 mg/kg/day and ceftazidime (dose not recorded). The dose of gentamicin was then titrated up to 17 mg/kg/day to give an adequate peak level of 9.3 mg/l (from 4.4 mg/l). Five days later he presented with lethargy, pallor and oliguria and a random gentamicin level was found to be 20 mg/l. Ultrasound showed echogenic kidneys of normal size. Renal function deteriorated and he required 10 days of haemodialysis. Post illness plasma creatinine was 39 µmol/l.

Discussion

All three patients were on a number of medications used routinely in patients with CF with few reported cases of acute renal failure. They came from different hospitals, which accounts for the variability in initial dosage[2]. The only child with evidence of abnormal liver function was case one who had macronodular cirrhosis noted on his ultrasound scan.

The risk of nephrotoxicity with aminoglycosides is well appreciated and CF guidelines suggest aminoglycoside levels are monitored around the third dose and then weekly, with baseline renal function checked at the start of therapy[1].

Nephrotoxicity in this group of patients may occur, particularly when aminoglycosides are used in combination with other antibiotics, resulting in potential complications such as tubulo-interstitial nephritis. Other risk factors are vomiting and dehydration. These points are well demonstrated in our three cases.

The combination of aminoglycosides with analgesics such as ibuprofen has been known to produce renal failure[3]. Ceftazidime and ciprofloxin have also been implicated in tubulo-interstitial nephritis[4,5]. Recent abstracts at international meetings have further highlighted the potential risks of combination treatment for *P. aeruginosa*[5–7]. The authors are also aware of four other children who required dialysis for acute renal failure in association with CF and antibiotic therapy within the last five years. Three had received a combination of ceftazidime and gentamicin and one had been treated with intravenous ceftazidime, tobramicin and oral

ibuprofen for associated arthritis (Email survey of British Association for Paediatric Nephrology members).

The practical implication of these reports is that CF patients receiving combination antibiotic therapy should have their plasma creatinine as well as aminoglycoside levels measured, at least weekly. This is particularly the case if there is a pre-existing renal abnormality (cases 1 and 2) or during a potentially dehydrating illness.

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