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Tetracycline Poisoning in Renal Failure

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Summary

Seven cases are reported in which drugs of the tetracycline group produced a fall in the glomerular filtration rate. In six patients there was a primary underlying renal disease and renal impairment. All seven patients were made seriously ill by the antibiotic. Two patients required immediate haemodialysis; one died and the other continued on dialysis until transplanted. Another patient initially responded to intravenous fluids and protein restriction but his renal function deteriorated and four months later he began maintenance haemodialysis. Three patients required peritoneal dialysis. The seventh patient responded satisfactorily to conservative management. The medical and medicolegal complications arising from the use of tetracycline in patients with renal disease are discussed. Yet another plea is made that drugs of the tetracycline group other than doxycycline should not be given to patients with chronic renal failure.

Introduction

Drugs of the tetracycline group may cause serious illness in patients with chronic renal failure. This fact was established 20 years ago (Bateman *et al.*, 1952; Womack *et al.*, 1952). Despite this and many subsequent confirmations (Shils, 1963; Wray *et al.*, 1965; Roth *et al.*, 1967; Hanson, 1968; Perkash *et al.*, 1969; Edwards *et al.*, 1970; George and Evans, 1971; Keenan *et al.*, 1973) patients continue to be admitted to hospital with severe exacerbations of renal failure produced by tetracycline. Two of the cases described below were admitted within a few weeks of the appearance of a leading article on the subject (*British Medical Journal*, 1972). This paper is written to show that tetracycline produces an impairment of renal function in patients with existing renal disease which is not always reversible and may be fatal.

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Case 1

A 31-year-old woman had suffered from Still's disease for 27 years. In 1954, at the age of 15, she was found to have amyloidosis and proteinuria with a blood urea of 22 mg/100 ml. By March 1969 the blood urea had risen to 77 mg/100 ml. In November 1969 she developed a urinary infection and a ureteric calculus which she passed spontaneously. Renal function had deteriorated, so that when she left hospital the blood urea was 160 mg/100 ml. In May 1970 she developed an infection of her gums and was treated with tetracycline 1 g/day by her dentist. She developed nausea, diarrhoea, lethargy, dyspnoea, and severe leg cramps. Six days after starting tetracycline she was admitted to hospital as an emergency case. She was dehydrated and hypotensive. The plasma sodium was 135 mEq, potassium 5·7 mEq, and bicarbonate 18 mEq/l.; and the blood urea was 315 mg and creatinine 9·1 mg/100 ml. A Teflon Silastic shunt was inserted into the left leg and haemodialysis performed. She remained very ill and within a few days her left foot became cold and white. A lumbar sympathectomy was performed, after which she required artificial ventilation, had a gastrointestinal haemorrhage, and died. Necropsy showed renal and hepatic amyloidosis, gastric ulceration, and pneumonia. There was no evidence of renal calculi or pyelonephritis.

Case 2

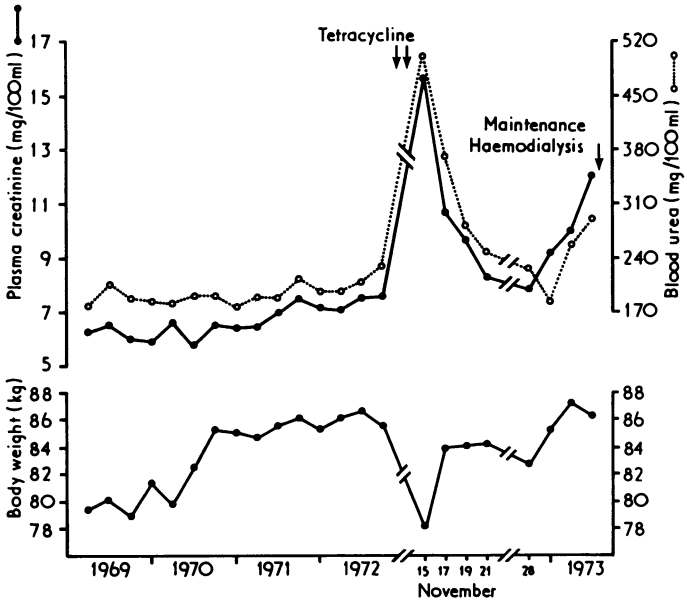
A 45-year-old man with polycystic kidneys was investigated in 1966. On a 20-g protein diet his blood urea was 66 mg/100 ml and his plasma creatinine 11·5 mg/100 ml. Two months later he developed sinusitis and was treated at home for five days with oxytetracycline 1 g/day. He developed nausea, vomiting, abdominal pain, and diarrhoea. He stopped the drug and came to hospital. The blood urea was 140 mg/100 ml and the plasma creatinine 14·8 mg/100 ml. He was treated with intravenous saline, antiemetics, and a low-protein diet. The symptoms improved after 48 hours but the plasma creatinine continued to rise and after 10 days maintenance haemodialysis was begun. Renal transplantation was performed three years later.

Case 3

This 33-year-old man presented in 1968 with vomiting, headaches, blurred vision, thirst, and nocturia. He was found to have hypertension with papilloedema. The plasma creatinine was 5 mg/100 ml and the blood urea 130 mg/100 ml. Renal arteriography showed left renal artery obstruction. At laparotomy this was found to be due to a fibrous band. When this was divided pulsation returned. Postoperatively he became oliguric and required haemodialysis for three to four weeks. Renal function then

improved and he was discharged on a 20-g protein diet. The blood urea was 124 mg/100 ml and the plasma creatinine 5·9 mg/100 ml. For four years he was treated as an outpatient. The hypertension was well controlled with methyldopa. He did not follow the diet and was eventually on a 70-80-g protein diet. During these four years the plasma creatinine rose only from 6·5 to 7·5 mg/100 ml and the blood urea from 180 to 220 mg/100 ml (see chart).

In November 1972 he developed influenza. His doctor prescribed oxytetracycline 1 g/day. After one week he returned to his doctor with weakness, anorexia, nausea, and vomiting. A further course of the same drug was supplied. A week later he was admitted to hospital. He was extremely dehydrated, his weight being 7·3 kg less than when last seen three months earlier. The blood pressure was 130/70 mm Hg. He was hyperpnoeic and his plasma bicarbonate was 9 mEq/l. The blood urea was 490 mg/100 ml and the plasma creatinine 15·6 mg/100 ml. He was treated with intravenous saline and sodium bicarbonate. When the vomiting stopped he was able to take a high-calorie, low-protein diet. He recovered slowly. On a normal diet at the time of discharge one month after admission his blood urea was 180 mg/100 ml and his plasma creatinine 9 mg/100 ml. During the next four months renal function deteriorated at a much faster rate than previously, and in April 1973 he was placed on maintenance haemodialysis.



Case 3. Rise in plasma creatinine and blood urea with accompanying weight loss induced by tetracycline in patient with chronic renal failure.

Case 4

A 38-year-old Ghanaian man was admitted to his local hospital with a three-day history of abdominal pain and vomiting. On clinical and biochemical grounds a diagnosis of acute pancreatitis was made. The blood urea was 180 mg/100 ml. He was treated with a "drip-and-suck" regimen which included intravenous tetracycline 2 g/day. He did not become anuric. After five days the blood urea rose to 400 mg/100 ml and he was flown to London. The intravenous infusion of tetracycline had continued uninterruptedly during the journey. When he arrived the blood urea was 600 mg/100 ml and the plasma creatinine 17·2 mg/100 ml. Tetracycline was stopped and peritoneal dialysis was begun. After 48 hours the blood urea fell to 200 mg/100 ml and thereafter he was managed with a high-calorie, low-protein diet and made a slow recovery. At the time of discharge six weeks after admission his blood urea was 41 mg/100 ml and his plasma creatinine 1·2 mg/100 ml.

Case 5

A 49-year-old Australian man had had chronic renal failure of unknown aetiology for two years. Immediately before sailing to England his plasma creatinine was 7 mg/100 ml and he developed dysuria and was given antibiotics. On the boat the treatment was changed to tetracycline 1 g/day. He came to hospital three days after landing, by which time he had been taking tetracycline for eight days. On admission he had hicups and excoriations and was jumpy and irritable. The blood urea was 309 mg/100 ml and the plasma creatinine 10·6 mg/100 ml. Despite treatment with intravenous saline and sodium bicarbonate the blood urea rose to 406 mg/100 ml and the plasma creatinine to 13·1 mg/100 ml. Peritoneal dialysis was begun and continued for 76 hours. At the end of this time the blood urea was still 200 mg/100 ml but he was then able to take a 20-g protein diet and made a gradual recovery. When discharged one month after admission his blood urea was 74 mg/100 ml his plasma creatinine 9·5 mg/100 ml.

Case 6

In February 1971 a 69-year-old man was investigated at another hospital for anorexia, nausea, and loss of weight. He was found to have proteinuria and a blood urea of 120 mg/100 ml. An appointment was made for him at this hospital but he went on holiday and developed acute bronchitis which was treated with oxytetracycline 1 g/day. Five days later he developed severe vomiting and was admitted here. On admission he was oliguric, with plasma sodium 147 mEq, potassium 7·4 mEq, and bicarbonate 14 mEq/l.; and a blood urea of 342 mg and a creatinine of 23·6 mg/100 ml. He was treated with peritoneal dialysis and developed pericarditis and gastrointestinal bleeding. He gradually improved, however, and was discharged six weeks after admission on a 30-g protein diet. The blood urea was 156 mg/100 ml and the plasma creatinine 9·9 mg/100 ml.

Case 7

In 1969 a 48-year-old woman was found to have retroperitoneal fibrosis and bilateral hydronephrosis. The obstruction was relieved by constructing an ileal conduit. She also suffered from diabetes mellitus, hypertension, and recurrent urinary tract infections. In 1970 the blood urea was 68 mg/100 ml and the plasma creatinine 2·3 mg/100 ml. In February 1972 renal function had shown little deterioration, with a blood urea of 70 mg/100 ml and a plasma creatinine of 2·5 mg/100 ml.

In November 1972 she developed fever, a non-productive cough, and retrosternal pain worsened by deep inspiration. Her doctor prescribed tetracycline 1 g/day. Next day she began vomiting and this persisted for three days. She then developed watery diarrhoea and was admitted to hospital two days later. The initial biochemical findings were: plasma sodium 132 mEq, potassium 3·1 mEq, and bicarbonate 9 mEq/l.; creatinine 5·3 mg, urea 145 mg, and glucose 265 mg/100 ml; and arterial pH 7·19. The urine was sterile. She was treated with intravenous saline, sodium bicarbonate, and potassium chloride. After one week the blood urea was 56 mg/100 ml and the plasma creatinine 3·9 mg/100 ml. In January 1973 the blood urea was 98 mg/100 ml and the plasma creatinine 3·1 mg/100 ml.

Discussion

The danger of prescribing tetracycline to patients with chronic renal failure is not generally appreciated. There is a misguided notion that in renal failure the administration of tetracycline may cause only a harmless and reversible rise in blood urea without reducing the glomerular filtration rate (Van Ypersele de Strihou, 1970; Dijkhuis and Van Meurs 1973). It is apparent from the cases described above that the adverse effects of tetracycline in renal failure are not uncommon and that the glomerular filtration rate is reduced, sometimes irreversibly. This view accords with the observations of others Wray *et al.*, 1965; Hanson, 1968; Perkash *et al.*, 1969; Eastwood, *et al.*, Edwards *et al.*, 1970; Brown, 1971; George and Evans, 1971; Curtis, 1972). Less severe effects of tetracyclines on the renal function of normal subjects have also been des-

cribed (Roth *et al.*, 1967). The impairment of renal function is quite distinct from the rarely-seen, Fanconi-like syndrome produced by a degradation product of tetracycline (anhydro-4-epitetracycline) formed from improper storage of tetracycline. This syndrome was harmless and fully reversible (Benitz and Diermeier, 1964).

There is a monotonous regularity in the sequence of clinical events associated with the prescribing of tetracycline to patients with chronic renal failure. The patient develops a minor infection, often respiratory; he seeks medical advice and is given tetracycline in normal amounts. He soon develops anorexia, nausea, and vomiting and sometimes diarrhoea. His condition rapidly deteriorates and he becomes dehydrated, hypotensive, and acidotic. He is then referred to hospital as an emergency case and often arrives still taking tetracycline. Treatment with intravenous saline and bicarbonate may suffice to control his symptoms but peritoneal dialysis may have to be performed. He may recover but renal function may remain so depressed that he has to be placed on maintenance haemodialysis.

There are a number of mechanisms by which tetracycline can affect renal function. Shils (1963) suggested that inhibition of intracellular protein synthesis occurs. This leads to decreased amino-acid utilization and subsequently to a rise in blood urea. Shils also noted that tetracyclines cause increased sodium excretion and a loss of weight. It is possible, therefore, that another cause for the rise in blood urea is a reduction in glomerular filtration rate due to volume depletion. Roth *et al.* (1967) reported a reduction in creatinine clearance and impaired ability to concentrate the urine in two out of six healthy subjects taking dimethylchlortetracycline. Other workers have reported a vasopressin-resistant diabetes insipidus associated with ingestion of this drug (Pijnenburg, 1966; Torin, 1967; Maxon and Rutsky, 1973). The use of tetracycline should therefore be avoided not only in patients with renal failure but also in those who are dehydrated, for it will increase the salt and water deficiency and ultimately produce renal failure. This point is well illustrated by case 4. It is probable that the patient developed acute renal failure as a complication of acute pancreatitis. Tetracycline cannot be blamed as the primary cause of the renal impairment but in view of its natriuretic and diuretic effects it may well have caused a further deterioration in renal function.

In addition to their metabolic effects tetracyclines may cause anorexia, nausea, vomiting, and diarrhoea. In renal failure the half life of these drugs (other than doxycycline) is increased (Kunin, 1967), so that the metabolic and gastrointestinal side effects will be more severe and prolonged. The deterioration in renal function produced in case 5 was not corrected by salt and water replacement, and 76 hours of peritoneal dialysis produced only a 50% fall in blood urea.

Two or three of our patients (cases 1, 6, and possibly 5) were given tetracycline by persons who were perhaps unaware of the presence of renal failure. We suggest that to safeguard such patients they should carry a card—"I am a patient with chronic renal failure. I must not be given the following drugs: tetracycline hydrochloride (Achromycin, Ambramycin, Clinitetrin, Co-Caps Tetracycline, Economycin, Steclin, Sustamycin, Telotrex, Tetrabid-Organon, Tetracyn, Totomycin); chlortetracycline hydrochloride (Aureomycin); oxytetracyline (Abbocin, Berkmycen, Clinimycin, Ethoxytet, Galenomycin, Imperacin, Oxydon, Oxymycin, Oxytetrin, Terramycin, Ticycline, Unimycin); dimethylchlortetracycline (Ledermycin); methacycline (Rondomycin); lymecycline (Armyl, Tetralysal)."

A number of preparations containing tetracyclines in combination with other drugs should also be added—for example, Lederstatin, Mysteclin (with nystatin); Terramycin S.F., Tetracyn S.F. (with vitamins). Other drugs could also be included on the card—for example, digoxin, ethacrynic acid, nitrofurantoin, chloramphenicol, phenformin.

Tetracyclines were prescribed to some of the patients described above in spite of the fact that all those concerned with the care of the patients were aware that they suffered from chronic renal failure. Cases 2 and 3 had well-documented advanced renal failure, and one of these patients (case 3), who had had stable renal function for four years, was given two consecutive courses of tetracycline. Both patients had to be treated with maintenance haemodialysis sooner than expected.

The increasing number of reports of the ill effects of tetracycline in patients with chronic renal failure raises the possibility that the continuation of this practice may eventually lead to medicolegal complications. Perhaps this would have more effect in publicizing this problem than the more usual forms of medical communication. There is now no reason for using the tetracyclines listed above for patients with renal failure. Doxycycline, which is one of the same group and has similar antibacterial properties and spectrum, does not cause a rise in blood urea (Little and Bailey, 1970) and has a half life in patients with renal failure equal to that in normal subjects (Mérier *et al.*, 1969-70; Mahon *et al.*, 1970).

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