Ease of Fixation.—Drilling the skull and inserting screws is technically simple and much easier than wiring or suturing methods, which involve dissection of the bone edge and the extradural space. The use of an onlay technique considerably reduces the operating time.

Good Tissue Acceptance.—Anodized titanium is an inert implant material. There is no reactive oedema of the scalp and no postoperative subgaleal effusion.

Dead Space.—Previous metal onlay techniques did not include provision for obliterating the dead space between the plate and the dura. When there is a large space a heat-cured acrylic resin mass can be processed to the tissue fitting surface of the plate (fig. 7).

Radiolucency.—An objection to most metallic plates is that they are radio-opaque. Titanium, however, is sufficiently radiolucent to allow radiological studies (see fig. 6).

Strength.—When titanium sheet is shaped to a formed contour it becomes rigid and will withstand considerable external force. As the plate is 0.5–1 cm "oversize," only an exceptional force would displace it inwards.

Lightness.—The density of titanium is low compared with that of other metals and alloys.

Sterilization.—Titanium plates and screws can be autoclaved. As most plastic materials need protection to prevent deformation due to stress relief on heating their sterility cannot be guaranteed.

Appendix

The anodizing solution is made up of 80% phosphoric acid, 10% sulphuric acid, and 10% water. The anode is titanium, voltage comes from a single phase rectified supply 0–120 V, and the current is about 10 A/ft².

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MEDICAL MEMORANDA

Hepatorenal Failure with Self-initiated Intermittent Rifampicin Therapy

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Continuous rifampicin therapy is considered to be relatively non-toxic. Nevertheless, complications associated with its intermittent administration have been reported (Campese *et al.*, 1973; Kleinknecht, 1972; Poole *et al.*, 1971; Girling *et al.*, 1971; Aquinas *et al.*, 1972). The symptoms include pyrexia, chills, arthralgia, jaundice, and acute renal failure. We report a case of combined hepatorenal failure in a patient who took rifampicin from time to time of her own accord.

Case Report

A 62-year-old European woman was admitted to hospital in September 1973 complaining of acute abdominal pain, nausea, vomiting, and chills. She was confused, but her history was later confirmed by her husband.

In April 1972 she was diagnosed as having active pulmonary tuberculosis. Three cachets of sodium aminosalicylate twice a day and rifampicin 450 mg daily were prescribed. She took these regularly until August 1973 when she developed severe heartburn and stopped both. Six days later she took three tablets of rifampicin. After two hours she developed chills, nausea, and vomiting, which resolved after 24 hours but left her lethargic for two weeks, during which she took no rifampicin. A fortnight after her first intermittent dose she took three tablets of rifampicin and some hours later she

developed nausea and malaise. Three days later she again took three tablets of rifampicin. This was rapidly followed by acute pain in the right loin, nausea, and vomiting. She had had severe dermatitis 39 years previously after a course of sulpha drugs. There was no pre-existing renal or liver disease.

On admission she was jaundiced and had a temperature of 38°C. No obvious abnormality was detected in the cardiovascular or respiratory system; the blood pressure was 140/80 mm Hg. She was almost anuric and was confused. Blood values were: bilirubin 4.3 mg/100 ml; Prothrombin time 60%; alkaline phosphatase 165 IU; SGOT 1,450 IU/ml; urea 106 mg/100 ml; creatinine 2.2 mg/100 ml; Hb 12.3 g/100 ml; E.S.R. 15 mm in 1 hour (Westergren). Reticulocyte counts were 1.4%, 1.5%, and 1.3% during the two weeks after admission. Urine microscopy showed white cells 13/high-power field, red blood cells 15/high-power field, no casts, and no protein. Nothing abnormal was seen on chest x-ray examination. Anti-streptolysin-O antistreptokinase, antihyaluronidase titres, and serum complement were all normal. Tests for L.E. cells and antinuclear factor gave negative results. These findings indicated hepatocellular damage and early acute renal failure with an absence of haemolysis. Liver function returned to normal after five days but the patient remained anuric and became progressively uraemic. The pain disappeared rapidly and its cause was never explained. Peritoneal dialysis was performed on the seventh day. Renal biopsy was not performed because glomerulonephritis seemed an unlikely diagnosis and she was treated as a case of acute tubular necrosis. Three days later she began a brisk diuresis and her renal function soon returned to normal.

Comment

Side effects of intermittent rifampicin therapy are well recognized (Aquinas *et al.*, 1972). One of the more well-defined syndromes is an influenza-like illness with pain and shock similar to that described by the patient. It is not widely known that intermittent rifampicin therapy can cause acute renal and hepatic failure, though workers in Scandinavia and Hong Kong have described transient minor abnormalities of liver function near the start of treatment (Aquinas *et al.*, 1972). The few reported cases of acute renal failure have occurred when an intermittent high dose of rifampicin has been deliberately prescribed. Acute tubular necrosis has been found on renal biopsy in two such patients (Aquinas *et al.*, 1972; Campese,

1973) and possibly shock hypotension are responsible for the acute oliguria. This may be mediated by an immune reaction, for patients on an intermittent regimen have high levels of circulating antirifampicin antibody (Aquinas *et al.*, 1972).

The patient's husband confirmed her history and we believed that it was authentic. She had been taking rifampicin and sodium aminosalicylate regularly for 16 months and suffered a severe reaction only after taking three intermittent doses of rifampicin. This is apparently the first report of combined hepatic and renal toxicity due to rifampicin, and it also seems to be the first report to incriminate rifampicin taken alone. There have been reports of immediate severe reactions with the first intermittent dose after a previous daily regimen (Kleinknecht *et al.*, 1972). Fortunately both the hepatic and renal toxic effects are re-

versible but physicians and patients need to be aware of the hazards of intermittent rifampicin therapy, even after a period of regular therapy.

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Acute Renal Failure and Rifampicin: Danger of Unsuspected Intermittent Dosage

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Adverse reactions to rifampicin seem to be less common when the drug is given continuously than when it is given intermittently. Patients may not take rifampicin continuously when it is so prescribed and thus may place themselves at risk. A case of acute renal failure related to unsuspected intermittent rifampicin dosage is described.

Case Report

The patient was a married woman aged 66 years. Proven axillary and cervical tuberculous lymphadenopathy had been present for 30 years and had been treated by excision and chemotherapy since 1953. In January 1971 further axillary involvement was treated with para-aminosalicylic acid and isoniazid and, for the first time, rifampicin. The same day she developed nausea, dizziness, diarrhoea, and incontinence of urine. She took no further rifampicin but concealed this from her doctor. After an outpatient visit she took rifampicin for the second time in June 1972 and on the same day again developed nausea, dizziness, diarrhoea, and incontinence of urine. This time she was more severely affected, and she collapsed while shopping and was admitted to hospital. She was found to have fever and leucocytosis but no definitive diagnosis was made and she recovered uneventfully. The patient took rifampicin for the third time in September 1973. The same symptoms occurred as previously and she was admitted to hospital. On admission she was febrile and was tender in the right hypochondrium. Blood urea was 121 mg/100 ml, having previously been known to be normal. Serum bilirubin was 4.7 mg/100 ml. On admission her temperature was 39.5°C but was normal for the next five days. On the sixth day after admission she was given a single dose of rifampicin after which there was a solitary temperature rise to 38.5°C and she became oliguric.

The patient was transferred to the renal unit six days later for renal dialysis. On examination she was obese, the skin was dry and lax, and the hair was coarse. Clinically no jaundice, anaemia, pigmentation, or

purpura were detectable. The jugular venous pressure was raised, and there was slight ankle and sacral oedema. Blood pressure was 180/100 mm Hg but there were no hypertensive changes in the retinal vessels. Apart from a poor memory for recent events there was no abnormality of the central nervous system. Chest x-ray film and electrocardiogram showed nothing abnormal. Plain x-ray examination of the abdomen showed enlarged renal outlines. High dose intravenous pyelography produced neither a nephrogram nor a pyelogram. The diagnosis of oliguric acute renal failure was confirmed and her condition was maintained by five haemodialyses. Diuresis occurred after 10 days of oliguria. The patient made a full clinical recovery and one month later renal function was grossly normal with an uncorrected creatinine clearance of 85 ml/min.

A left renal biopsy done during the oliguric phase showed essentially normal glomeruli and tubules. There was interstitial oedema and some lymphocytes were seen in the interstitium but the appearances were not considered such as to warrant a diagnosis of interstitial nephritis. Tests for Australia antigen gave negative results. Serum and urinary levels of fibrin degradation products were not raised. Liver function test results were normal, immunoglobulin IgM, IgA, and IgG were normal, and serum complement (C3) was normal. The urine initially contained an excess of white and red blood cells but later became normal. Antibodies to rifampicin were not measured.

Discussion

The combination of fever, dizziness, nausea, diarrhoea, and incontinence of urine, while curious, was strikingly consistent after each ingestion of rifampicin. It is interesting that the symptoms occurred, albeit mildly, after the first dose. We are uncertain of the cause of the renal failure, and dehydration and transient hyperbilirubinaemia may have been contributory. There was no evidence of soluble complex disease, intravascular coagulation, or interstitial nephritis. Poole *et al.* (1971 a) showed rifampicin-dependent antibodies in patients on intermittent dosage and attributed symptoms to the interaction of high serum antibody levels with the re-introduced antigen. Other cases of acute renal failure have been described by Poole *et al.* (1971 b), Kleinknecht *et al.* (1972), and Campese *et al.* (1973).

This case illustrates the importance of ensuring that rifampicin is taken continuously and that patients are warned not to restart the drug without supervision if it has been discontinued.

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