REFERENCES


Pulmonary Tuberculosis in Patient on Intermittent Haemodialysis

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It is not surprising that tuberculosis should sometimes complicate chronic renal failure with its associated anaemia and malnutrition. Treatment of this infection is likely to be hindered both by the patient's general medical state and by specific pharmacological problems owing to altered excretion of the drugs used.

It is well known (Welch, 1954) that streptomycin appears in the urine after parenteral administration. However, recovery varies between 30% and 80% of the dose and alternative metabolic pathways must exist (Kunin, 1966). Isoniazid also appears in the urine under normal circumstances (Welch, 1954), but again recovery is incomplete and there is no information about its serum half-life in oliguric patients (Kunin, 1967). The fact that para-aminosalicylic acid (P.A.S.) is excreted by the kidneys is acknowledged by the use of the ferric chloride test to detect its presence in urine. However, Kunin (1967) states that this is not the only excretory pathway and that some of the drug is destroyed in the liver.

These observations confirm that major pharmacological problems are likely to arise during the treatment of patients with tuberculosis and severe renal impairment, and Kunin (1966) has suggested that P.A.S. is best avoided altogether in these circumstances. Therefore when a patient with this combination of conditions presented for treatment the opportunity was taken to investigate the metabolism of these drugs.

METHODS

Streptomycin.—A standard tube dilution technique and the Oxford staphylococcus were used. The results were compared with levels given in the literature (Welch, 1954).

P.A.S.—Use was made of the Bratton and Marshall (1939) technique. Proteins were removed with 20% trichloroacetic acid. Standards were made up in pooled sera. The results were compared with levels given in the literature (Emerson and Kuper, 1964) and with results obtained in a normal subject.

Isoniazid and its metabolites were separated from P.A.S. by using the solvent extraction technique of Peters (1960). Free isoniazid was measured by the method of Short (1954) by means of a Unicam SP, 800, employing scale expansion $\times 5$ on a Bristol recorder. The method of Peters (1960) was used to check the levels of "total" hydrazides. The results were compared with levels given in the literature (Peters, 1960) and with the results obtained in a normal subject.

CASE REPORT

A 37-year-old housewife presented in September 1967 complaining of increasing fatigue for six months. Apart from anaemia (haemoglobin 5.5 g./100 ml.) and mild hypertension (180/100) there were no abnormal findings. Her urine contained protein but no excess of cells and was sterile on routine and Löwenstein–Jensen cultures. Investigations showed the presence of severe renal failure (blood urea 410 mg./100 ml., creatinine clearance 1.5 ml./min.). Cystoscopy and retrograde pyelography showed no abnormalities apart from a slight reduction in kidney size.

Her urinary output remained less than 1,000 ml./24 hours and she was started on peritoneal dialysis while being considered for regular dialysis treatment. After she had been accepted for this, closer attention was paid to a partly calcified opacity in the right lung, which had been obscured by the medial end of the clavicle. Tomography of the lesion showed a small cavity, and examination of her sputum confirmed the diagnosis of open pulmonary tuberculosis.

In view of this she was treated in a single room adjacent to a general medical ward and not in the intermittent dialysis unit. A recirculating single pass machine (R.S.P. Travenol) containing a twin coil with a surface area of 1.45 sq. m. was used. Access to the circulation was obtained via a Teflon Silastic shunt in her left forearm. Three seven-hour daytime dialyses were performed each week and she was encouraged to eat a high calorie high protein (100 g.) diet. Approximately 1 pint (570 ml.) of blood was given each week, so as to maintain a haematocrit in the 25–30% range. During treatment her urine output averaged 300 ml./day. Treatment of her tuberculosis was started with streptomycin, P.A.S., and isoniazid in doses which were modified according to the blood levels obtained. Isoniazid was given daily, initially in a dose of 300 mg., but after three weeks this was reduced to 150 mg.; pyridoxine 20 mg. daily was given as well. Streptomycin was given intramuscularly after each dialysis, usually in a dose of 0.75 g. After five weeks, during which time she had received a total of 11 g., she complained of vertigo, and caloric tests confirmed the presence of vestibular damage. By this time the organism was known to be sensitive to all three drugs and the streptomycin was withdrawn. P.A.S. was also given only after each dialysis; initially a dose of 6 g. was used but later this was reduced to 3 g.

After eight weeks' treatment acid-fast bacilli could no longer be seen in the sputum, and three weeks later she was transferred to the intermittent dialysis unit. There, twice weekly, overnight haemodialyses of 16 hours' duration were carried out on a Kill dialyser. The dose of isoniazid was not changed, but it was necessary to reduce the dose of P.A.S. to 2 g. after each dialysis—that is, 4 g./week. Her satisfactory progress continued, and in January 1968 further tomograms of the right apex showed that her cavity had closed.

RESULTS

The results are shown graphically in Figs. 1–3.

Streptomycin.—After an intramuscular dose of 1 g. (equivalent to 20 mg./kg. body weight) a peak blood level of 16 µg./ml. was obtained at two hours. The plasma half-life was about 20 hours.
**Isoniazid**.—After an oral dose of 150 mg. (equivalent to 3 mg./kg. body weight), the blood level continued to rise for eight hours to a peak of 270 μg./100 ml. before falling slowly. The plasma half-life was about 17 hours. A significant fall in plasma level was observed across the dialyser.

P.A.S.—After an oral dose of 6 g. (equivalent to 100 mg./kg. body weight) the level rose steadily to 100 mg./100 ml. at about 24 hours and remained at this level until the next dialysis. A significant fall in level was observed across the dialyser, and some of the drug was recovered from the dialysate.

**DISCUSSION**

Three-weekly dialysis was adopted during the early stages of treatment because of the observation (Davidson and Pendras, 1967) that this allows a more liberal diet and results in the more rapid rehabilitation of patients with chronic renal failure than does the conventional twice-weekly regimen. The R.S.P. dialyser was used rather than the Kiil, since it permitted relatively short day-time dialysis to be supervised by the nursing staff of a general ward with a doctor on call in the hospital. This did not give rise to any problems.

The blood levels of streptomycin are hard to explain, since they are not significantly different from those obtained in subjects with normal renal function. Despite this the patient developed vestibular damage after a total dose of only 11 g. The method of measurement used records levels of 2, 4, 8, 16, and 32 μg./ml. and it is possible that an error in one tube could lead to a false peak value of half the true value. However, estimations were made on several occasions with different doses of streptomycin. A constant pattern was obtained and it is suggested that in our patient the alternative metabolic pathways mentioned earlier were unusually active.

The isoniazid levels confirm that the presence of renal failure delays the disappearance of the drug from the blood stream. None the less, alternative routes of elimination are obviously important. Because of the possibility of accumulation of the drug, pyridoxine was given prophylactically from the outset and no signs of toxicity were observed. The fact that the drug is dialysable was confirmed.

P.A.S., on the other hand, appears to be excreted solely by the kidney. Very small doses were required, and after the change from coil to Kiil dialysis the patient complained of tinnitus on several occasions. This was associated with blood levels of up to 120 mg./100 ml. Provided blood levels are measured, P.A.S. would appear, contrary to the suggestion of Kunin (1966), to be a most satisfactory drug for the treatment of tuberculosis in the presence of impaired renal function. In fact, renal failure gives the patient a distinct advantage over others who have to take 12 g. of P.A.S. daily.

Increasing facilities for the treatment of patients with end-stage renal disease by dialysis or by renal transplantation are bound to lead to the need to treat more patients with tuberculosis. The immunosuppressive drugs may make the problem more difficult still.

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